=> b reg
FILE 'REGISTRY' ENTERED AT 09:01:50 ON 01 SEP 2004

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 30 AUG 2004 HIGHEST RN 736108-36-4
DICTIONARY FILE UPDATES: 30 AUG 2004 HIGHEST RN 736108-36-4

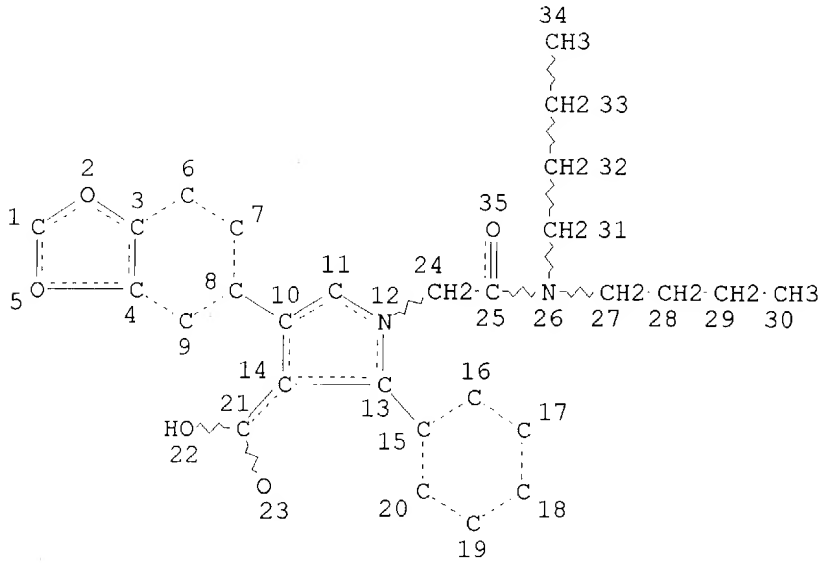
TSCA INFORMATION NOW CURRENT THROUGH MAY 21, 2004

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=> d que l8
L6 STR



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CONNECT IS E1 RC AT 23
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

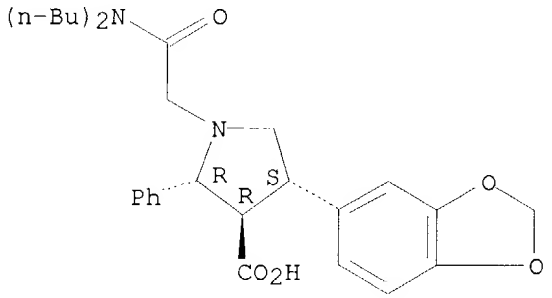
GRAPH ATTRIBUTES:
RSPEC 12 15 8
NUMBER OF NODES IS 35

STEREO ATTRIBUTES: NONE
L8 1 SEA FILE=REGISTRY SSS FUL L6

=> d ide

L8 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2004 ACS on STN
RN 178608-57-6 REGISTRY
CN 3-Pyrrolidinecarboxylic acid, 4-(1,3-benzodioxol-5-yl)-1-[2-(dibutylamino)-2-oxoethyl]-2-phenyl-, (2R,3R,4S)-rel- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 3-Pyrrolidinecarboxylic acid, 4-(1,3-benzodioxol-5-yl)-1-[2-(dibutylamino)-2-oxoethyl]-2-phenyl-, (2α,3β,4α)-
FS STEREOSEARCH
MF C28 H36 N2 O5
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

Relative stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

6 REFERENCES IN FILE CA (1907 TO DATE)
6 REFERENCES IN FILE CAPLUS (1907 TO DATE)

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FILE 'HOME' ENTERED AT 09:02:01 ON 01 SEP 2004

=>

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=> b hcaplus
FILE 'HCAPLUS' ENTERED AT 11:06:16 ON 01 SEP 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)
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FILE COVERS 1907 - 1 Sep 2004  VOL 141 ISS 10
FILE LAST UPDATED: 31 Aug 2004  (20040831/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

'OBI' IS DEFAULT SEARCH FIELD FOR 'HCAPLUS' FILE

=> d que l9 nos
L6              STR
L8            1 SEA FILE=REGISTRY SSS FUL L6
L9            6 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L8


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L9   ANSWER 1 OF 6  HCAPLUS  COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER:         2002:171682  HCAPLUS
DOCUMENT NUMBER:          136:232311
TITLE:                    Preparation of 4-benzoheterocyclyl-1-
                          aminocarbonylmethylpyrrolidine-3-carboxylic acid
                          derivatives as endothelin antagonists
INVENTOR(S):              Winn, Martin; Boyd, Steven A.; Hutchins, Charles W.;
                          Hwan-Soo, Jae; Tasker, Andrew S.; Von Geldern, Tomas
                          W.; Kester, Jeffrey; Sorensen, Bryan K.;
                          Szczepankiewicz, Bruce G.; Henry, Kenneth; Liu, Gang;
                          Wittenberger, Steven J.; King, Steven A.; Janus, Todd
                          J.; Padley, Robert J.
PATENT ASSIGNEE(S):       Abbott Laboratories, USA
SOURCE:                   PCT Int. Appl., 817 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.          KIND   DATE        APPLICATION NO.         DATE
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     WO 2002017912        A1    20020307    WO 2001-US27220         20010831
         W:  CA, JP, MX
         RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
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-PT, SE, TR
PRIORITY APPLN. INFO.: US 2000-653563 A 20000831
OTHER SOURCE(S): MARPAT 136:232311
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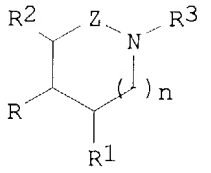

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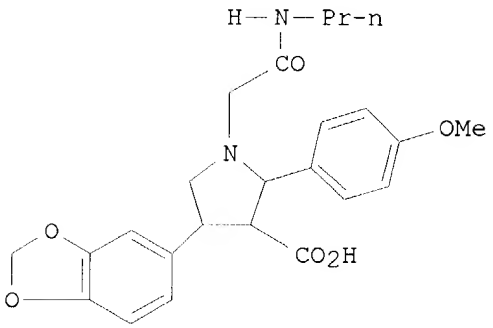


II

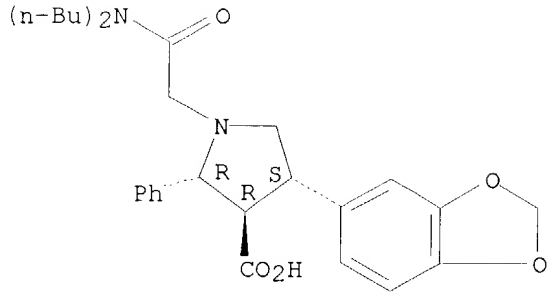
AB Title compds. [I; n = 0; Z = CH2; R = CO2H; R1 = alkoxyaryl, alkoxyalkoxyaryl, heterocyclylalkyl; R2 = 1,3-benzodioxyl, 4-benzofuranyl, 5-indanyl; R3 = R4R5CO; R4 = R6R7N, R8R9NNH; R5 = methylene; one of R6, R7 is H, the other is arylalkyl, diarylalkyl; one of R8, R9 is alkyl, the other is aryl] stereoisomers, and pharmaceutically acceptable salts are prepared as endothelin antagonists. Thus, the title compound II was prepared from Et (4-methoxybenzoyl)acetate, 5-(2-nitrovinyl)-1,3-benzodioxol, ethyldiisopropylamine, and N-Pr bromoacetamide and was in vitro tested for binding effect to the endothelin receptor and the determination of title compound as functional ET antagonist.

IT **178608-57-6P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of 4-benzoheterocyclyl-1-aminocarbonylmethylpyrrolidine-3-carboxylic acid derivs. as endothelin antagonists)

RN 178608-57-6 HCAPLUS
CN 3-Pyrrolidinecarboxylic acid, 4-(1,3-benzodioxol-5-yl)-1-[2-(dibutylamino)-2-oxoethyl]-2-phenyl-, (2R,3R,4S)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

Searched by P. Ruppel



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 2 OF 6 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:891585 HCAPLUS
DOCUMENT NUMBER: 134:42122
TITLE: Preparation of substituted pyrrolidine-3-carboxylic acids as endothelin antagonists
INVENTOR(S): Winn, Martin; Boyd, Steven A.; Hutchins, Charles W.; Jae, Hwan-soo; Tasker, Andrew S.; Von Geldern, Thomas W.; Kester, Jeffrey A.; Sorensen, Bryan K.; Szczepankiewicz, Bruce G.; Henry, Kenneth J.; Liu, Gang; Wittenberger, Steven J.; King, Steven A.
PATENT ASSIGNEE(S): Abbott Laboratories, USA
SOURCE: U.S., 587 pp., Cont.-in-part of U.S. Ser. No. 794,506.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6162927	A	20001219	US 1997-905913	19970804
US 5767144	A	19980616	US 1995-442575	19950530
ZA 9701179	A	19980115	ZA 1997-1179	19970212
NZ 514171	A	20031031	NZ 1997-514171	19970212
WO 9906397	A2	19990211	WO 1998-US15479	19980727
WO 9906397	A3	19991209		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
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AU 748469	B2	20020606		
EP 1003740	A2	20000531	EP 1998-937139	19980727
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, FI, RO				
TR 200000993	T2	20001221	TR 2000-200000993	19980727
JP 2001512119	T2	20010821	JP 2000-505155	19980727
BR 9815296	A	20011120	BR 1998-15296	19980727

TR 200101233	T2	20020621	TR 2001-200101233		19980727
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NZ 502395	A	20020828	NZ 1998-502395		19980727
ZA 9806908	A	19990426	ZA 1998-6908		19980731
TW 552260	B	20030911	TW 1998-87112783		19980810
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BG 104216	A	20001229	BG 2000-104216		20000302
US 6462194	B1	20021008	US 2000-572493		20000515
US 6380241	B1	20020430	US 2000-714934		20001117
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			US 1996-600625	B2	19960213
			US 1997-794506	A2	19970204
			NZ 1997-503365	A1	19970212
			US 1997-905913	A	19970804
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OTHER SOURCE(S): MARPAT 134:42122

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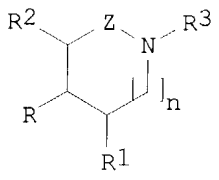

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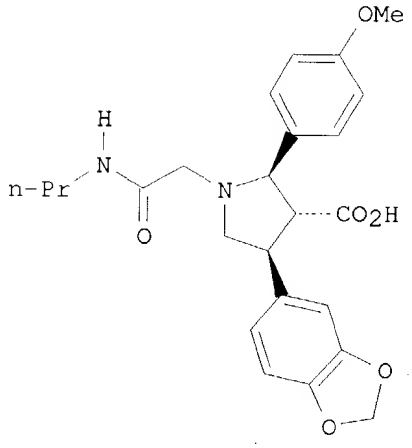


II

AB The title compds. {I; Z = CR18R19, CO (wherein R18, R19 = H, alkyl); n = 0-1; R = (CH2)mW [m = 0-6; W = CO2G (G = H, a carboxy protecting group), PO3H2, CN, etc.]; R1, R2 = H, alkyl, alkenyl, etc.; R3 = -R5COR4, -NR6R5COR4, -R7SO2R6, etc. [R5 = a bond, alkylene, alkenylene, etc.; R4, R6 = NR11R12 (R11, R12 = H, alkyl, haloalkyl, etc.), alkyl, alkenyl, etc.; R7 = a bond, alkylene, alkenylene, etc.]}, useful for antagonizing endothelin, were prepared and formulated. E.g., a multi-step synthesis of trans,trans-II which showed 96.4% endothelin A inhibition at 1 μM, was given.

IT **178608-57-6P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

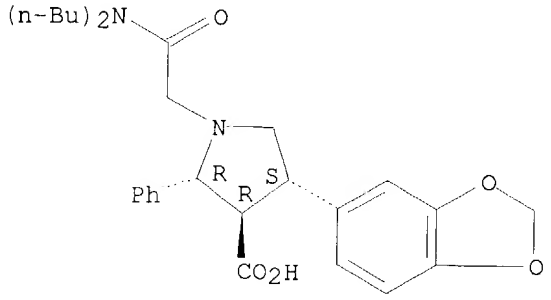
Searched by P. Ruppel

(preparation of substituted pyrrolidine-3-carboxylic acids as endothelin antagonists)

RN 178608-57-6 HCAPLUS

CN 3-Pyrrolidinecarboxylic acid, 4-(1,3-benzodioxol-5-yl)-1-[2-(dibutylamino)-2-oxoethyl]-2-phenyl-, (2R,3R,4S)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 3 OF 6 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1999:113673 HCAPLUS

DOCUMENT NUMBER: 130:182352

TITLE: Preparation of substituted pyrrolidine-3-carboxylic acids as endothelin antagonists

INVENTOR(S): Winn, Martin; Boyd, Steven A.; Hutchins, Charles W.; Jae, Hwan-Soo; Tasker, Andrew S.; Von Geldern, Thomas W.; Kester, Jeffrey A.; Sorensen, Bryan K.; Szczepankiewicz, Bruce G.; Henry, Kenneth J.; Liu, Gang; Wittenberger, Steven J.; King, Steven A.

PATENT ASSIGNEE(S): Abbott Laboratories, USA

SOURCE: PCT Int. Appl., 821 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 5

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9906397	A2	19990211	WO 1998-US15479	19980727
WO 9906397	A3	19991209		
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RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6162927	A	20001219	US 1997-905913	19970804
AU 9885921	A1	19990222	AU 1998-85921	19980727
AU 748469	B2	20020606		
EP 1003740	A2	20000531	EP 1998-937139	19980727
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JP 2001512119	T2	20010821	JP 2000-505155		19980727
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NZ 502395	A	20020828	NZ 1998-502395		19980727
NO 2000000542	A	20000404	NO 2000-542		20000202
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PRIORITY APPLN. INFO.:			US 1997-905913	A	19970804
			US 1998-48955	A	19980327
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			US 1995-442575	A2	19950530
			US 1995-497998	B2	19950802
			US 1996-600625	B2	19960213
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OTHER SOURCE(S): MARPAT 130:182352

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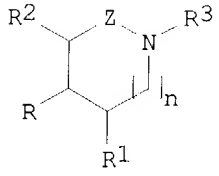

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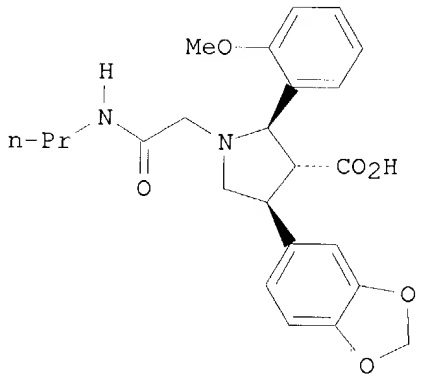


II

AB The title compds. [I; Z = CR18R19, C(O) (wherein R18, R19 = H, lower alkyl); n = 0-1; R = CN, OH, alkoxy, etc.; R1, R2 = H, lower alkyl, alkenyl, etc.; R3 = R4C(O)R5-, R4R5a-, R4C(O)R5NR6- (wherein R5 = a bond, alkylene, alkenylene, etc.; R5a = alkylene, alkenylene; R4, R6 = H, lower alkyl, haloalkyl, etc.), etc.], useful in treatment of conditions such as hypertension, congestive heart failure, atherosclerosis, etc., were prepared and formulated. E.g., a 4-step synthesis of the title compound trans,trans-II which showed 96.4% inhibition of ETA at 1 μM, was given.

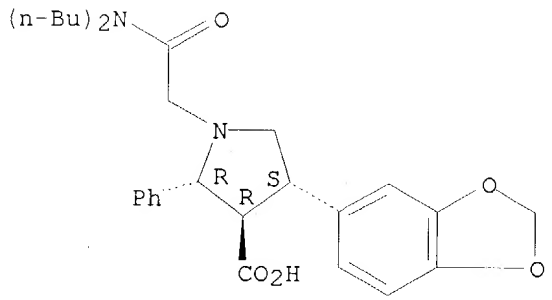
IT **178608-57-6P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of substituted pyrrolidine-3-carboxylic acids as endothelin antagonists)

RN 178608-57-6 HCAPLUS

CN 3-Pyrrolidinecarboxylic acid, 4-(1,3-benzodioxol-5-yl)-1-[2-(dibutylamino)-2-oxoethyl]-2-phenyl-, (2R,3R,4S)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L9 ANSWER 4 OF 6 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:414738 HCAPLUS
DOCUMENT NUMBER: 129:95396
TITLE: Preparation of 1-(carbamoylmethyl)pyrrolidine-3-carboxylates and analogs as endothelin antagonists
INVENTOR(S): Winn, Martin; Boyd, Steven A.; Hutchins, Charles W.; Jae, Hwan-Soo; Tasker, Andrew S.; Von Geldern, Thomas W.; Kester, Jeffrey A.; Sorensen, Bryan K.
PATENT ASSIGNEE(S): Abbott Laboratories, USA
SOURCE: U.S., 109 pp., Cont.-in-part of U.S. Ser. No. 334,717, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5767144	A	19980616	US 1995-442575	19950530
US 5622971	A	19970422	US 1995-457935	19950601
US 5731434	A	19980324	US 1995-458094	19950601
CA 2195677	AA	19960229	CA 1995-2195677	19950804
WO 9606095	A1	19960229	WO 1995-US9924	19950804
W: AU, CA, JP, KR, MX				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9532137	A1	19960314	AU 1995-32137	19950804
AU 711832	B2	19991021		
EP 776324	A1	19970604	EP 1995-928323	19950804
EP 776324	B1	20020612		
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JP 10504565	T2	19980506	JP 1995-508101	19950804
EP 1186603	A2	20020313	EP 2001-125462	19950804
EP 1186603	A3	20030709		
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AT 219077	E	20020615	AT 1995-928323	19950804
PT 776324	T	20021129	PT 1995-928323	19950804
ES 2179881	T3	20030201	ES 1995-928323	19950804
IL 114894	A1	20030410	IL 1995-114894	19950810
NZ 514171	A	20031031	NZ 1997-514171	19970212
US 6162927	A	20001219	US 1997-905913	19970804
HK 1008328	A1	20030207	HK 1998-109192	19980715
AU 9920344	A1	19990603	AU 1999-20344	19990310
AU 725122	B2	20001005		

US 6462194	B1	20021008	US 2000-572493	20000515
US 6380241	B1	20020430	US 2000-714934	20001117
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OTHER SOURCE(S): MARPAT 129:95396

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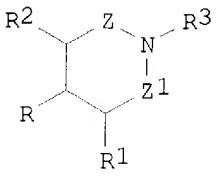

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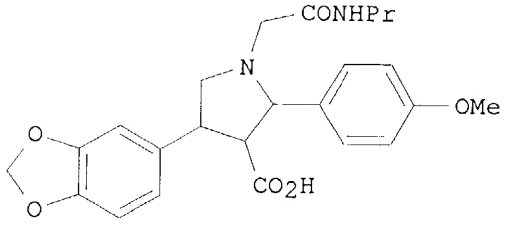


II

AB Title compds. [I; R = (CH2)mR4; R1,R2 = H, (un)substituted alkyl, heterocyclyl, aryl, etc.; R3 = acyl(alkyl), etc.; R4 = OH, alkoxy, acyl, heterocyclyl, etc.; Z = CH2, CO, alkylidene; Z1 = bond or CH2; m = 0-6] were prepared Thus, 4-(MeO)C6H4COCH2CO2Et was alkylated by 5-(2-nitrovinyl)-1,3-benzodioxole and the product reductively cyclized to give, in 3 addnl. steps, title compound II. Data for biol. activity of I were given.

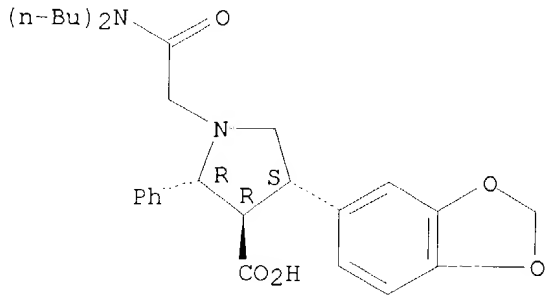
IT **178608-57-6P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of 1-(carbamoylmethyl)pyrrolidine-3-carboxylates and analogs as endothelin antagonists)

RN 178608-57-6 HCAPLUS

CN 3-Pyrrolidinecarboxylic acid, 4-(1,3-benzodioxol-5-yl)-1-[2-(dibutylamino)-2-oxoethyl]-2-phenyl-, (2R,3R,4S)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



Searched by P. Ruppel

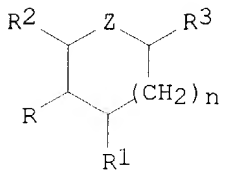
REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 5 OF 6 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:568105 HCAPLUS
DOCUMENT NUMBER: 127:248099
TITLE: Preparation of benzo-1,3-dioxolyl- and benzofuranyl-substituted pyrrolidine derivatives as endothelin antagonists.
INVENTOR(S): Winn, Martin; Boyd, Steven A.; Hutchins, Charles W.; Jae, Hwan-soo; Tasker, Andrew S.; Von Geldern, Thomas W.; Kester, Jeffrey A.; Sorensen, Bryan K.; Szczepankiewicz, Bruce G.; Henry, Kenneth J., Jr.; Liu, Gang; Wittenberger, Steven J.; King, Steven A.
PATENT ASSIGNEE(S): Abbott Laboratories, USA
SOURCE: PCT Int. Appl., 682 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9730045	A1	19970821	WO 1997-US1936	19970212
W: AU, BR, CA, CN, CZ, HU, IL, JP, KR, MX, NZ				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2245587	AA	19970821	CA 1997-2245587	19970212
AU 9722620	A1	19970902	AU 1997-22620	19970212
ZA 9701179	A	19980115	ZA 1997-1179	19970212
EP 885215	A1	19981223	EP 1997-905816	19970212
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
CN 1219172	A	19990609	CN 1997-192184	19970212
CN 1091768	B	20021002		
BR 9707509	A	19990727	BR 1997-7509	19970212
NZ 330818	A	20000526	NZ 1997-330818	19970212
JP 2002504081	T2	20020205	JP 1997-529397	19970212
CN 1384100	A	20021211	CN 2002-104623	20020209

PRIORITY APPLN. INFO.: US 1996-600625 A 19960213
US 1997-794506 A 19970204
WO 1997-US1936 W 19970212

OTHER SOURCE(S): MARPAT 127:248099
GI



I

AB Title compds. [I; Z = CR18R19, CO; R18, R19 = H, alkyl; n = 0, 1; R =

(CH2)mW; m = 0-6; W = (protected) CO2H, PO3H2, cyano, alkylaminocarbonyl, tetrazolyl, OH, alkoxy, sulfonamido, specified heterocyclyl, etc.; R1 = alkyl, alkenyl, haloalkyl, haloalkoxyalkyl, cycloalkylalkyl, alkylsulfonylamidoalkyl, heterocyclylalkyl, etc.; R2 = H, alkyl, alkenyl, alkynyl, alkoxyalkyl, cycloalkyl, alkoxycarbonylalkyl, hydroxyalkyl, aminocarbonylalkenyl, hydroxyalkenyl, aryloxyalkyl, etc.; R3 = R4COR5, R6SO2R7, etc.; R5, R7 = bond, alkylene, alkenylene, iminoalkylene, etc.; R4, R6 = amino, haloalkyl, cycloalkyl, alkoxyalkyl, arylalkyl, haloalkenyl, haloalkynyl, etc.], were prepared Thus, trans,trans-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-cyclopropylmethyl-N-propylaminocarbonylmethyl)pyrrolidine-3-carboxylic acid (preparation given) inhibited [125I]ET-1 binding to receptors by 100% at 1 mM.

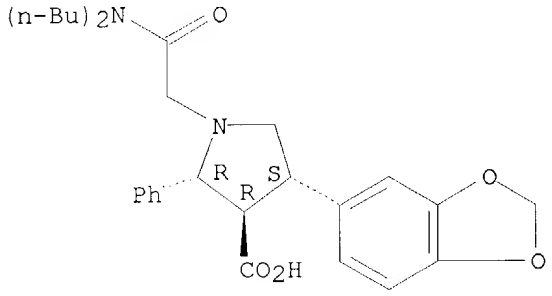
IT **178608-57-6P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of benzo-1,3-dioxolyl- and benzofuranyl-substituted pyrrolidine derivs. as endothelin antagonists)

RN 178608-57-6 HCAPLUS

CN 3-Pyrrolidinecarboxylic acid, 4-(1,3-benzodioxol-5-yl)-1-[2-(dibutylamino)-2-oxoethyl]-2-phenyl-, (2R,3R,4S)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L9 ANSWER 6 OF 6 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1996:428406 HCAPLUS

DOCUMENT NUMBER: 125:86623

TITLE: Preparation of pyrrolidinecarboxylic acid derivatives and analogs as endothelin antagonists

INVENTOR(S): Winn, Martin; Boyd, Steven A.; Hutchins, Charles W.; Jae, Hwan-Soo; Tasker, Andrew S.; Vongeldern, Thomas W.; Kester, Jeffrey A.; Sorensen, Bryan K.

PATENT ASSIGNEE(S): Abbott Laboratories, USA

SOURCE: PCT Int. Appl., 277 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 5

PATENT INFORMATION:

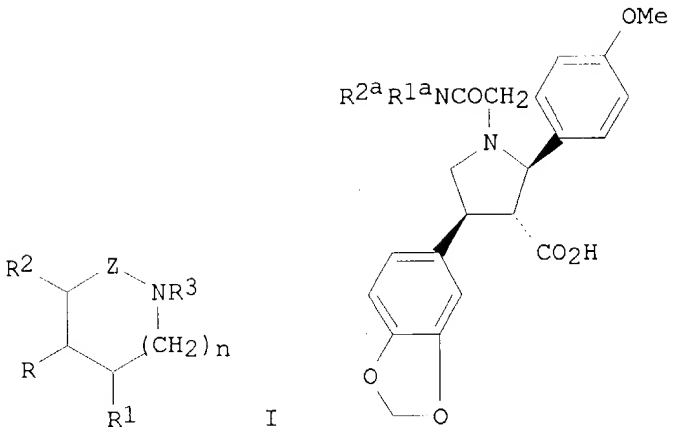
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9606095	A1	19960229	WO 1995-US9924	19950804

W: AU, CA, JP, KR, MX
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

US 5767144	A	19980616	US 1995-442575		19950530
AU 9532137	A1	19960314	AU 1995-32137		19950804
AU 711832	B2	19991021			
EP 776324	A1	19970604	EP 1995-928323		19950804
EP 776324	B1	20020612			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE					
JP 10504565	T2	19980506	JP 1995-508101		19950804
AT 219077	E	20020615	AT 1995-928323		19950804
NZ 514171	A	20031031	NZ 1997-514171		19970212
HK 1008328	A1	20030207	HK 1998-109192		19980715
PRIORITY APPLN. INFO.:			US 1994-293349	A	19940819
			US 1994-334717	A	19941104
			US 1995-442575	A	19950530
			US 1995-497998	A	19950802
			WO 1995-US9924	W	19950804
			NZ 1997-503365	A1	19970212

OTHER SOURCE(S): MARPAT 125:86623

GI



AB The title compds. [I; Z = CR18R19, CO; wherein R18, R19 = H, lower alkyl; n = 0,1; R = (CH2)mW; wherein m = 0-6; W = (un)protected CO2H, P(O)(OH)2, P(O)(OH)E (wherein E = H, lower alkyl, arylalkyl), cyano, CONHR17 (wherein R17 = lower alkyl), alkylaminocarbonyl, dialkylaminocarbonyl, tetrazolyl, OH, alkoxy, sulfamido, CONHSO2R16 (R16 = lower alkyl, haloalkyl, Ph, dialkylamino), etc.; R1, R2 = H, lower alkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxycarbonylalkyl, hydroxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, aminocarbonylalkyl, mono- or dialkylaminocarbonylalkyl, aminocarbonylalkenyl, mono- or dialkylaminocarbonylalkenyl, hydroxyalkenyl, aryl, arylalkoxyalkyl, heterocyclyl, etc.; provided that one of R1 and R2 is other than H; R3 = R4COZ5, R6SO2Z7, R26SOZ27, etc.; wherein Z5 = bond, alkylene, alkenylene, N-(un)substituted NH-alkylene or alkylene-NH-alkylene; Z7 = bond, alkylene, alkenylene, N-(un)substituted NH-alkylene; R4, R6 = (un)substituted NH2, lower alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, alkoxyalkyl; R26 = lower alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl,

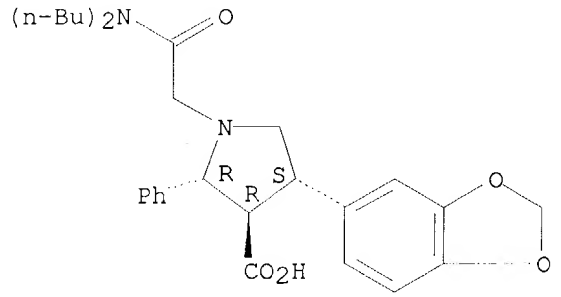
alkoxyalkyl, alkoxyhaloalkyl; Z27 = alkylene, alkenylene] or pharmaceutically acceptable salts thereof are prepared These compds. are useful for the treatment of hypertension, congestive heart failure, restenosis following arterial injury, cerebral or myocardial ischemia, or atherosclerosis. Thus, addition reaction of Et (4-methoxybenzoyl)acetate with 5-(2-nitrovinyl)-1,3-benzodioxole in the presence of DBU in toluene at 80° for 75 min gave Et 2-(4-methoxybenzoyl)-4-nitromethyl-3-(1,3-benzodioxol-5-yl)butyrate which underwent hydrogenation in the presence of a Raney nickel 2800 catalyst in EtOH at 4 atm H pressure to give Et 2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-4,5-dihydro-3H-pyrrole-3-carboxylate . Reduction of the latter compound with NaBH3CN in the presence of bromocresol in THF under adding dropwise a mixture of concentrated HCl and EtOH gave a mixture of cis,cis-, trans,trans-, and cis,trans-Et 2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)pyrrolidine-3-carboxylate which underwent alkylation with N-propylbromoacetamide in the presence of (Me2CH)2NEt in MeCN at 50° for 1 h followed by selective saponification with NaOH in aqueous EtOH and acidification with HCl to give the title compound (II; R1a = H, R2a = n-Pr). The latter compound and II (R1a = R2a = Bu) at 1 μM in vitro inhibited 96.4 and 99.2%, resp., binding of [125I]endothelin 1 to endothelin A receptor in a membrane preparation from MMQ cell line (prolactin secreting rat pituitary cells).

IT **178608-57-6P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of pyrrolidinecarboxylic acid derivs. and analogs as endothelin antagonists for disease therapy)

RN 178608-57-6 HCAPLUS

CN 3-Pyrrolidinecarboxylic acid, 4-(1,3-benzodioxol-5-yl)-1-[2-(dibutylamino)-2-oxoethyl]-2-phenyl-, (2R,3R,4S)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



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=>

Connecting via Winsock to STN

Welcome to STN International! Enter x:x

LOGINID:ssspat01plr

PASSWORD:
* * * * * * RECONNECTED TO STN INTERNATIONAL * * * * * *
SESSION RESUMED IN FILE 'HOME' AT 11:19:41 ON 01 SEP 2004
FILE 'HOME' ENTERED AT 11:19:41 ON 01 SEP 2004

=> => b medl
FILE 'MEDLINE' ENTERED AT 11:21:00 ON 01 SEP 2004

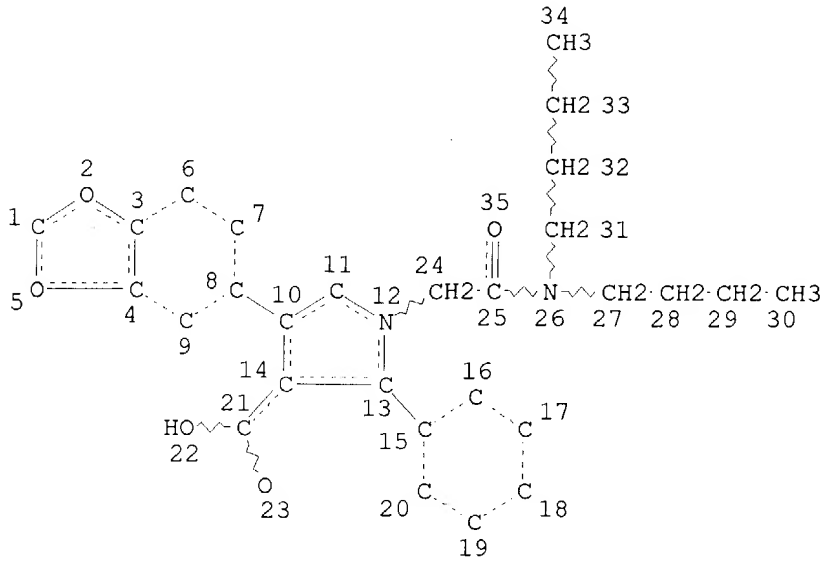
FILE LAST UPDATED: 31 AUG 2004 (20040831/UP). FILE COVERS 1951 TO DATE.

On February 29, 2004, the 2004 MeSH terms were loaded. See HELP RLOAD for details. OLDMEDLINE now back to 1951.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2004 vocabulary. See http://www.nlm.nih.gov/mesh/ and http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html for a description of changes.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d que l11
L6 STR



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CONNECT IS E2 RC AT 6

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CONNECT IS E2  RC AT   7
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CONNECT IS E2  RC AT  17
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CONNECT IS E1  RC AT  23
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC  12  15   8
NUMBER OF NODES IS  35

STEREO ATTRIBUTES: NONE
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L11            0 SEA FILE=MEDLINE ABB=ON  PLU=ON  L8


=> b embase
FILE 'EMBASE' ENTERED AT 11:21:11 ON 01 SEP 2004
COPYRIGHT (C) 2004 Elsevier Inc. All rights reserved.

 FILE COVERS 1974 TO 26 Aug 2004 (20040826/ED)

 EMBASE has been reloaded. Enter HELP RLOAD for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> d que l12 nos
L6               STR
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L12            0 SEA FILE=EMBASE ABB=ON  PLU=ON  L8


=> b biosis
FILE 'BIOSIS' ENTERED AT 11:21:20 ON 01 SEP 2004
Copyright (c) 2004 The Thomson Corporation.

FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 26 August 2004 (20040826/ED)

FILE RELOADED: 19 October 2003.

=> d que l13 nos
L6               STR
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L13            0 SEA FILE=BIOSIS ABB=ON  PLU=ON  L8


=> b cancerlit
FILE 'CANCERLIT' ENTERED AT 11:21:32 ON 01 SEP 2004
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FILE COVERS 1963 TO 15 Nov 2002 (20021115/ED)

On July 28, 2002, CANCERLIT was reloaded. See HELP RLOAD for details.

CANCERLIT thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2002 vocabulary. Enter HELP THESAURUS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

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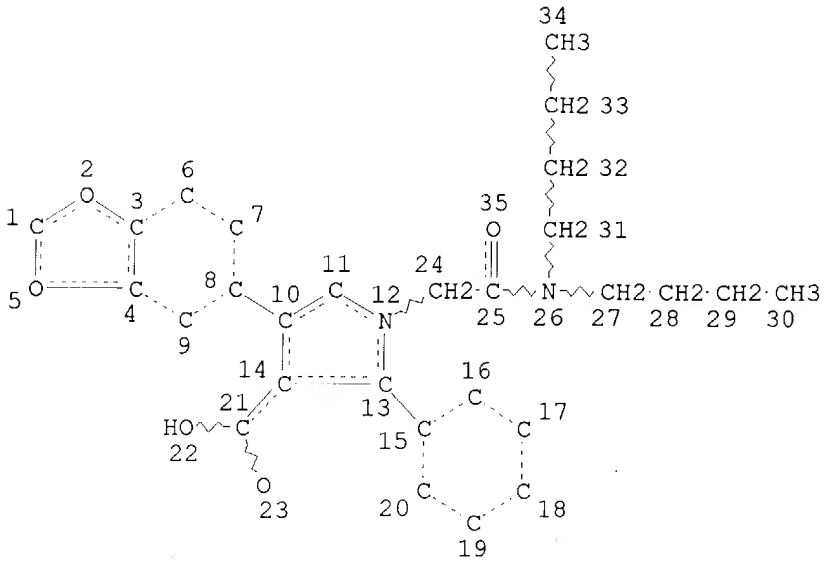
L6 STR



NODE ATTRIBUTES:
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CONNECT IS E2 RC AT 6
CONNECT IS E2 RC AT 7
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CONNECT IS E2 RC AT 17
CONNECT IS E2 RC AT 18
CONNECT IS E2 RC AT 19
CONNECT IS E2 RC AT 20
CONNECT IS E1 RC AT 23
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC 12 15 8
NUMBER OF NODES IS 35

STEREO ATTRIBUTES: NONE
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L14 0 SEA FILE=CANCERLIT ABB=ON PLU=ON L8

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 FILE LAST UPDATED: 31 AUG 2004 (20040831/UP). FILE COVERS 1951 TO DATE.

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 for details. OLDMEDLINE now back to 1951.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2004 vocabulary. See http://www.nlm.nih.gov/mesh/ and
 http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html for a
 description of changes.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> d que l137
L98        42603 SEA FILE=MEDLINE ABB=ON  PLU=ON  "PROSTATIC NEOPLASMS"/CT
L99         6745 SEA FILE=MEDLINE ABB=ON  PLU=ON  L98(L)DT
L107         424 SEA FILE=MEDLINE ABB=ON  PLU=ON  BICALUTAMIDE
L112         241 SEA FILE=MEDLINE ABB=ON  PLU=ON  L107 AND L99
L137         131 SEA FILE=MEDLINE ABB=ON  PLU=ON  L112 AND PY<=2000


=> d que l138
L65 (          1)SEA FILE=REGISTRY ABB=ON  PLU=ON  NILUTAMIDE/CN
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L99         6745 SEA FILE=MEDLINE ABB=ON  PLU=ON  L98(L)DT
L109         201 SEA FILE=MEDLINE ABB=ON  PLU=ON  NILUTAMIDE OR L65
L114         116 SEA FILE=MEDLINE ABB=ON  PLU=ON  L109 AND L99
L138          99 SEA FILE=MEDLINE ABB=ON  PLU=ON  L114 AND PY<=2000


=> d que l139
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L99         6745 SEA FILE=MEDLINE ABB=ON  PLU=ON  L98(L)DT
L115       33098 SEA FILE=MEDLINE ABB=ON  PLU=ON  L67 OR PREDNISONE
L116          87 SEA FILE=MEDLINE ABB=ON  PLU=ON  L115 AND L99
L139          61 SEA FILE=MEDLINE ABB=ON  PLU=ON  L116 AND PY<=2000


=> d que l140
L98        42603 SEA FILE=MEDLINE ABB=ON  PLU=ON  "PROSTATIC NEOPLASMS"/CT
L99         6745 SEA FILE=MEDLINE ABB=ON  PLU=ON  L98(L)DT
L118        3687 SEA FILE=MEDLINE ABB=ON  PLU=ON  HYDROCORTISONE/CT(L)TU
L119          24 SEA FILE=MEDLINE ABB=ON  PLU=ON  L99 AND L118
L140          22 SEA FILE=MEDLINE ABB=ON  PLU=ON  L119 AND PY<=2000


=> d que l141
L98        42603 SEA FILE=MEDLINE ABB=ON  PLU=ON  "PROSTATIC NEOPLASMS"/CT
L99         6745 SEA FILE=MEDLINE ABB=ON  PLU=ON  L98(L)DT
L120        1837 SEA FILE=MEDLINE ABB=ON  PLU=ON  KETOCONAZOLE/CT(L)TU
L121          58 SEA FILE=MEDLINE ABB=ON  PLU=ON  L99 AND L120
L141          56 SEA FILE=MEDLINE ABB=ON  PLU=ON  L121 AND PY<=2000


=> d que l142
L98        42603 SEA FILE=MEDLINE ABB=ON  PLU=ON  "PROSTATIC NEOPLASMS"/CT
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L99          6745 SEA FILE=MEDLINE ABB=ON  PLU=ON  L98(L)DT
L123           57 SEA FILE=MEDLINE ABB=ON  PLU=ON  ("CYPROTERONE ACETATE"/CT(L)TU
                  ) AND L99
L142           45 SEA FILE=MEDLINE ABB=ON  PLU=ON  L123 AND PY<=2000


=> d que l143
L98         42603 SEA FILE=MEDLINE ABB=ON  PLU=ON  "PROSTATIC NEOPLASMS"/CT
L99          6745 SEA FILE=MEDLINE ABB=ON  PLU=ON  L98(L)DT
L124          348 SEA FILE=MEDLINE ABB=ON  PLU=ON  (FLUTAMIDE/CT(L)TU) AND L99
L143          293 SEA FILE=MEDLINE ABB=ON  PLU=ON  L124 AND PY<=2000


=> d que l144
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L99          6745 SEA FILE=MEDLINE ABB=ON  PLU=ON  L98(L)DT
L125        25596 SEA FILE=MEDLINE ABB=ON  PLU=ON  "VITAMIN D"+NT/CT
L126           44 SEA FILE=MEDLINE ABB=ON  PLU=ON  (L125(L)TU) AND L99
L144           17 SEA FILE=MEDLINE ABB=ON  PLU=ON  L126 AND PY<=2000


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L99          6745 SEA FILE=MEDLINE ABB=ON  PLU=ON  L98(L)DT
L127        48031 SEA FILE=MEDLINE ABB=ON  PLU=ON  ESTROGENS+NT/CT
L128         1028 SEA FILE=MEDLINE ABB=ON  PLU=ON  (L127(L)TU) AND L99
L145          985 SEA FILE=MEDLINE ABB=ON  PLU=ON  L128 AND PY<=2000


=> d que l146
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L129          155 SEA FILE=MEDLINE ABB=ON  PLU=ON  (GOSERELIN/CT(L)TU) AND L99
L146           97 SEA FILE=MEDLINE ABB=ON  PLU=ON  L129 AND PY<=2000


=> d que l147
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L99          6745 SEA FILE=MEDLINE ABB=ON  PLU=ON  L98(L)DT
L131           11 SEA FILE=MEDLINE ABB=ON  PLU=ON  (PROGESTERONE/CT(L)TU) AND
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L147           11 SEA FILE=MEDLINE ABB=ON  PLU=ON  L131 AND PY<=2000


=> d que l148
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L130          163 SEA FILE=MEDLINE ABB=ON  PLU=ON  (LEUPROLIDE/CT(L)TU) AND L99
L148          107 SEA FILE=MEDLINE ABB=ON  PLU=ON  L130 AND PY<=2000


=> d all l137 3 5 6   bicalutamide

L137 ANSWER 3 OF 131     MEDLINE on STN
AN   2001068333     MEDLINE
DN   PubMed ID: 11025427
TI   Antagonist/agonist balance of the nonsteroidal antiandrogen
     bicalutamide (Casodex) in a new prostate cancer model.
AU   Hobisch A; Hoffmann J; Lambrinidis L; Eder I E; Bartsch G; Klocker H;
     Culig Z
```

CS Department of Urology, University of Innsbruck, Austria..
alfred.hobisch@uibk.ac.at
SO Urologia internationalis, **(2000)** 65 (2) 73-9.
Journal code: 0417373. ISSN: 0042-1138.
CY Switzerland
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200012
ED Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001227
AB Androgen ablation is standard therapy for advanced prostate carcinoma. It can be administered either as a monotherapy or as a combined androgen blockade. In the present study we have investigated molecular mechanisms which are responsible for the development of resistance to therapy in advanced prostate cancer. For this purpose, we have cultured LNCaP cells in steroid-depleted medium for 1 year. The newly generated subline LNCaP-abl was characterized. In early passages (<75) LNCaP-abl cells showed a biphasic hypersensitive response to androgenic stimulation. Passages later than 75 are inhibited by androgen. Proliferation of LNCaP-abl cells was stimulated by the pure nonsteroidal antiandrogen **bicalutamide** (Casodex). To improve our understanding of changes which occur during intermittent androgen ablation, we have generated the sublines LNCaP-R (reversal; cultured with fetal calf serum) and LNCaP-RA (reversal and androgen; cultured with fetal calf serum and androgen) from LNCaP-abl cells. In both cell lines an increase of the basal proliferation rate was observed. Androgen receptor expression in LNCaP-abl cells was 4-fold higher than that in parental LNCaP cells (4.7 vs. 1.2 fmol/microg protein). Androgen receptor content in LNCaP-R cells was 1.8 fmol/microg protein and in LNCaP-RA cells 1.0 fmol/microg protein. The basal androgen receptor activity was 30-fold higher in LNCaP-abl cells compared to that in parental LNCaP cells. This basal activity was reduced in LNCaP-RA cells. Both androgen and the nonsteroidal androgen receptor antagonist hydroxyflutamide induced a 2- to 4-fold higher activation of androgen receptor in LNCaP-abl than in LNCaP cells. There was a switch from an antagonist to an agonist of the nonsteroidal antiandrogen **bicalutamide** (Casodex) in LNCaP-abl cells. Antagonistic properties of this androgen receptor blocker were again observed in both sublines (LNCaP-R and LNCaP-RA) derived from LNCaP-abl cells. In concordance with proliferation data in vitro, growth of LNCaP-abl cells in nude mice was stimulated by **bicalutamide.** In contrast, supplementation of androgen led to inhibition of proliferation of these cells. The present study provides new information that is useful for a better understanding of therapy-refractory prostate cancer. It is also important for the development of new therapy strategies for advanced carcinoma of the prostate.

CT Check Tags: Human; Male; Support, Non-U.S. Gov't
*Androgen Antagonists: TU, therapeutic use
*Androgens: AG, agonists
*Anilides: TU, therapeutic use
***Prostatic Neoplasms: DT, drug therapy**
Tumor Cells, Cultured
RN **90357-06-5 (bicalutamide)**
CN 0 (Androgen Antagonists); 0 (Androgens); 0 (Anilides)

L137 ANSWER 5 OF 131 MEDLINE on STN
AN 2001031593 MEDLINE
DN PubMed ID: 11025708

TI **Bicalutamide** monotherapy compared with castration in patients with nonmetastatic locally advanced prostate cancer: 6.3 years of followup.
AU Iversen P; Tyrrell C J; Kaisary A V; Anderson J B; Van Poppel H; Tammela T L; Chamberlain M; Carroll K; Melezinek I
CS Rigshospitalet, University of Copenhagen, Copenhagen, Denmark.
SO Journal of urology, **(2000 Nov)** 164 (5) 1579-82.
Journal code: 0376374. ISSN: 0022-5347.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 200011
ED Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001121
AB PURPOSE: Nonsteroidal antiandrogen monotherapy may be a treatment option for some patients with advanced prostate cancer. We report a survival and safety update from an analysis of 2 studies in which patients with nonmetastatic (M0) locally advanced disease were treated with either 150 mg. **bicalutamide** monotherapy or castration. MATERIALS AND METHODS: Data from 2 open label, multicenter studies of identical design were pooled according to protocol. Patients with stage T3/4 prostate cancer were randomized to receive 150 mg. **bicalutamide** daily or castration (orchiectomy or 3.6 mg. goserelin acetate every 28 days) in a 2:1 ratio. RESULTS: A total of 480 patients with locally advanced prostate cancer were randomized to treatment. After a median followup of 6.3 years mortality was 56%. There was no statistically significant difference between the 2 groups in overall survival (hazard ratio 1.05, upper 1-sided 95% confidence limit 1.31, p = 0.70) or time to progression (1.20, 1.45, p = 0.11). There were statistically significant benefits in the **bicalutamide** monotherapy group in the 2 quality of life parameters of sexual interest (p = 0.029) and physical capacity (p = 0.046). The highest incidences of adverse events were the pharmacological side effects of hot flashes in the castration group, and breast pain and gynecomastia in the **bicalutamide** group. The incidences of other types of adverse events were low. **Bicalutamide** was well tolerated, with few drug related withdrawals from study, and no new safety issues were identified during this longer followup. CONCLUSIONS: Monotherapy with 150 mg. **bicalutamide** is an attractive alternative to castration in patients with locally advanced prostate cancer for whom immediate hormone therapy is indicated.
CT Check Tags: Comparative Study; Human; Male; Support, Non-U.S. Gov't
*Androgen Antagonists: TU, therapeutic use
*Anilides: TU, therapeutic use
*Castration
Disease Progression
Follow-Up Studies
Multicenter Studies
***Prostatic Neoplasms: DT, drug therapy**
Prostatic Neoplasms: MO, mortality
*Prostatic Neoplasms: SU, surgery
Randomized Controlled Trials
Survival Analysis
RN **90357-06-5 (bicalutamide)**
CN 0 (Androgen Antagonists); 0 (Anilides)

L137 ANSWER 6 OF 131 MEDLINE on STN
AN 2001008175 MEDLINE
DN PubMed ID: 10853458

TI New indication sought for **bicalutamide.**
AU Anonymous
SO Oncology (Williston Park, N.Y.), **(2000 May)** 14 (5) 654, 772.
Journal code: 8712059. ISSN: 0890-9091.
CY United States
DT News Announcement
LA English
FS Priority Journals
EM 200010
ED Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001025
CT Check Tags: Human; Male
Androgen Antagonists: AE, adverse effects
Androgen Antagonists: PD, pharmacology
*Androgen Antagonists: TU, therapeutic use
Anilides: AE, adverse effects
Anilides: PD, pharmacology
*Anilides: TU, therapeutic use
Antineoplastic Agents, Hormonal: AE, adverse effects
Antineoplastic Agents, Hormonal: PD, pharmacology
*Antineoplastic Agents, Hormonal: TU, therapeutic use
Antineoplastic Combined Chemotherapy Protocols: TU, therapeutic use
Castration
Chemotherapy, Adjuvant
Neoadjuvant Therapy
***Prostatic Neoplasms: DT, drug therapy**
Quality of Life
Randomized Controlled Trials
RN **90357-06-5 (bicalutamide)**
CN 0 (Androgen Antagonists); 0 (Anilides); 0 (Antineoplastic Agents, Hormonal); 0 (Antineoplastic Combined Chemotherapy Protocols)

=> d all l138 1 2 3

L138 ANSWER 1 OF 99 MEDLINE on STN
AN 2000512716 MEDLINE
DN PubMed ID: 11071217
TI Androgen blockade in prostate cancer.
CM Comment on: Lancet. 2000 Apr 29;355(9214):1491-8. PubMed ID: 10801170
AU Labrie F; Candas B
SO Lancet, **(2000 Jul 22)** 356 (9226) 341-2.
Journal code: 2985213R. ISSN: 0140-6736.
CY ENGLAND: United Kingdom
DT Commentary
Letter
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 200011
ED Entered STN: 20010322
Last Updated on STN: 20011004
Entered Medline: 20001128
CT Check Tags: Human; Male
*Androgen Antagonists: TU, therapeutic use
Cyproterone Acetate: TU, therapeutic use
*Flutamide: TU, therapeutic use
*Imidazoles: TU, therapeutic use
Meta-Analysis
Orchiectomy

***Prostatic Neoplasms: DT, drug therapy**
RN 13311-84-7 (Flutamide); 427-51-0 (Cyproterone Acetate); **63612-50-0 (nilutamide)**
CN 0 (Androgen Antagonists); 0 (Imidazoles)

L138 ANSWER 2 OF 99 MEDLINE on STN
AN 2000259108 MEDLINE
DN PubMed ID: 10801170
TI Maximum androgen blockade in advanced prostate cancer: an overview of the randomised trials. Prostate Cancer Trialists' Collaborative Group.
CM Comment in: ACP J Club. 2001 Jan-Feb;134(1):23
Comment in: Lancet. 2000 Apr 29;355(9214):1474-5. PubMed ID: 10801162
Comment in: Lancet. 2000 Jul 22;356(9226):341-2. PubMed ID: 11071217
AU Anonymous
SO Lancet, **(2000 Apr 29)** 355 (9214) 1491-8.
Journal code: 2985213R. ISSN: 0140-6736.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
(META-ANALYSIS)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 200005
ED Entered STN: 20000606
Last Updated on STN: 20011004
Entered Medline: 20000522
AB BACKGROUND: In advanced prostate cancer, androgen suppression (AS) by surgery or drugs controls testicular hormone secretion, and the further addition of an antiandrogen such as **nilutamide**, flutamide, or cyproterone acetate is referred to as maximum androgen blockade (MAB). The aim of this overview was to compare the effects on the duration of survival of MAB and of AS alone. METHODS: The collaborative meta-analysis of 27 randomised trials involved central reanalysis of the data on each of 8275 men (98% of those ever randomised in trials of MAB vs AS) with metastatic (88%) or locally advanced (12%) prostate cancer. Half were over 70 years of age, and follow-up was typically for about 5 years. FINDINGS: 5932 (72%) men have died; of the deaths for which causes were provided, about 80% were attributed to prostate cancer. 5-year survival was 25.4% with MAB versus 23.6% with AS alone, a non-significant gain of 1.8% (SE 1.3; logrank 2p=0.11). There was no significant heterogeneity in the treatment effect (MAB vs AS) with respect to age or disease stage. The results for cyproterone acetate, which accounted for only a fifth of the evidence, appeared slightly unfavourable to MAB (5-year survival 15.4% MAB vs 18.1% AS alone; difference -2.8% [SE 2.4]; logrank 2p=0.04 adverse), whereas those for **nilutamide** and flutamide appeared slightly favourable (5-year survival 27.6% MAB vs 24.7% AS alone; difference 2.9% [SE 1.3]; logrank 2p=0.005). Non-prostate-cancer deaths (although not clearly significantly affected by treatment) accounted for some of the apparently adverse effects of cyproterone acetate. INTERPRETATION: In advanced prostate cancer, addition of an antiandrogen to AS improved the 5-year survival by about 2% or 3% (depending on whether the analysis includes or excludes the cyproterone acetate trials), but the range of uncertainty as to the true size of this benefit runs from about 0% to about 5%.
CT Check Tags: Human; Male; Support, Non-U.S. Gov't
Aged
*Androgen Antagonists: TU, therapeutic use
*Cyproterone: TU, therapeutic use
*Flutamide: TU, therapeutic use
*Imidazoles: TU, therapeutic use
Orchiectomy

***Prostatic Neoplasms: DT, drug therapy**
Prostatic Neoplasms: MO, mortality
Prostatic Neoplasms: SU, surgery
Randomized Controlled Trials
Survival Analysis
RN 13311-84-7 (Flutamide); 2098-66-0 (Cyproterone); **63612-50-0 (nilutamide)**
CN 0 (Androgen Antagonists); 0 (Imidazoles)

L138 ANSWER 3 OF 99 MEDLINE on STN
AN 2000138748 MEDLINE
DN PubMed ID: 10673793
TI Antiandrogens: a summary review of pharmacodynamic properties and tolerability in prostate cancer therapy.
AU Migliari R; Muscas G; Murru M; Verdacchi T; De Benedetto G; De Angelis M
CS Operative Unit of Urology, ASL 8, Arezzo, Italy.. uromig@tin.it
SO Archivio italiano di urologia, andrologia : organo ufficiale [di] Societa italiana di ecografia urologica e nefrologica / Associazione ricerche in urologia, **(1999 Dec)** 71 (5) 293-302. Ref: 65
Journal code: 9308247. ISSN: 1124-3562.
CY Italy
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200002
ED Entered STN: 20000314
Last Updated on STN: 20000314
Entered Medline: 20000229
AB This article provides a summary of the pharmacodynamic properties of major antiandrogens as well as an extensive review of their tolerability. Presently there are two classes of androgen receptor antagonists: the so-called pure, non-steroidal antiandrogens which include flutamide, **nilutamide** and the more recent bicalutamide and the steroidal antiandrogens cyproterone acetate, megestrol acetate and WIN 49596. Although non steroidal and steroidal compounds have been found to be equally effective in the treatment of prostate cancer presently no studies comparing the use of steroidal or non steroidal antiandrogens with chemical or surgical castration have evaluated quality of life per se. The only advantage of cyproterone acetate on pure antiandrogens seems to be the low incidence of hot flushes; a commonly reported adverse effect of androgen ablative therapy. However, hepatotoxicity associated with long term daily doses of 300 mg daily and the unacceptably high incidence of cardiovascular side effects (10%) should restrict its use to patients who are intolerant of pure antiandrogen compound. In contrast to steroidal compound nonsteroidal compounds let sexual potency to be retained, which is an important consideration with respect to the quality of life of some patients and, at present, the main indication for monotherapy with the pure antiandrogens. As regard as pure antiandrogens clinically important adverse events including gastrointestinal events, particularly diarrhea and occasional disturbances of liver function related to flutamide treatment and antabuse effect, problems with light-dark adaptation and rare interstitial pneumonitis related to **nilutamide** indicates the bicalutamide, due to its better tolerability profile, together with its once-daily oral administration regimen, could be considered the antiandrogen of first choice in the treatment of prostatic cancer.
CT Check Tags: Human; Male
*Androgen Antagonists: PD, pharmacology
*Androgen Antagonists: TU, therapeutic use

Anilides: PD, pharmacology
Anilides: TU, therapeutic use
Antineoplastic Agents, Hormonal: PD, pharmacology
Antineoplastic Agents, Hormonal: TU, therapeutic use
Flutamide: PD, pharmacology
Flutamide: TU, therapeutic use
Imidazoles: PD, pharmacology
Imidazoles: TU, therapeutic use
***Prostatic Neoplasms: DT, drug therapy**
Receptors, Androgen: AI, antagonists & inhibitors
RN 13311-84-7 (Flutamide); **63612-50-0 (nilutamide)**; 90357-06-5 (bicalutamide)
CN 0 (Androgen Antagonists); 0 (Anilides); 0 (Antineoplastic Agents, Hormonal); 0 (Imidazoles); 0 (Receptors, Androgen)

=> d all l139 2 3 5

L139 ANSWER 2 OF 61 MEDLINE on STN
AN 2001192615 MEDLINE
DN PubMed ID: 11205458
TI Chemotherapy in advanced androgen-independent prostate cancer 1990-1999: a decade of progress?.
AU Culine S; Droz J P
CS Department of Medicine, CRLC Val d'Aurelle, Montpellier, France.. stculine@valdorel.fnclcc.fr
SO Annals of oncology : official journal of the European Society for Medical Oncology / ESMO, **(2000 Dec)** 11 (12) 1523-30. Ref: 74
Journal code: 9007735. ISSN: 0923-7534.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200104
ED Entered STN: 20010410
Last Updated on STN: 20010410
Entered Medline: 20010405
AB BACKGROUND AND PURPOSE: A great number of clinical research studies have been reported in the field of chemotherapy for advanced androgen-independent prostate cancer during the last ten years. The aims of the present review were to assess their impact on management of the disease and on survival of patients. METHODS: The review of full published reports was facilited by the use of a MEDLINE computer search. RESULTS: Clinical research studies have focused on defining guidelines for eligibility criteria and accurate endpoints for patients to be enrolled onto clinical trials and developing new agents or combination of drugs including estramustine phosphate. Any combination of current chemotherapy has no impact on overall survival of patients. Among drugs in development, only the promising activity observed with docetaxel deserves randomized trials to assess its impact on survival. The major innovative advance of the 90s is the demonstration of the impact of chemotherapy (mitoxantrone + **prednisone**) on quality of life as compared to **prednisone** alone. A greater and longer-lasting improvement in quality of life along with a concomitant decrease in costs was observed. CONCLUSIONS: At the present time, chemotherapy should be considered as a palliative treatment in patients with symptomatic androgen-independent disease. The enrollment of patients into clinical trials dealing with quality of life as primary endpoint is strongly solicited. A standard

methodology should be used in phase II trials with a primary goal of selection of agents which should progress to randomized trials using survival as an endpoint. Hopefully new specific strategies targeted to reverse the molecular changes that underlie prostate tumorigenesis should rapidly impact the multimodality management of AIPC in the third millenium.

CT Check Tags: Human; Male
Antineoplastic Agents, Hormonal: TU, therapeutic use
Antineoplastic Agents, Phytogenic: TU, therapeutic use
*Antineoplastic Combined Chemotherapy Protocols: TU, therapeutic use
Mitoxantrone: TU, therapeutic use
Neoplasm Metastasis
*Paclitaxel: AA, analogs & derivatives
Paclitaxel: TU, therapeutic use
Palliative Care
Prednisolone: TU, therapeutic use
***Prostatic Neoplasms: DT, drug therapy**
Prostatic Neoplasms: PA, pathology
*Quality of Life
Randomized Controlled Trials
*Taxoids

RN 114977-28-5 (docetaxel); 33069-62-4 (Paclitaxel); 50-24-8 (Prednisolone); 65271-80-9 (Mitoxantrone)

CN 0 (Antineoplastic Agents, Hormonal); 0 (Antineoplastic Agents, Phytogenic); 0 (Antineoplastic Combined Chemotherapy Protocols); 0 (Taxoids)

L139 ANSWER 3 OF 61 MEDLINE on STN

AN 2000217012 MEDLINE

DN PubMed ID: 10751862

TI Prostate specific antigen response to mitoxantrone and **prednisone** in patients with refractory prostate cancer: prognostic factors and generalizability of a multicenter trial to clinical practice.

AU Dowling A J; Czaykowski P M; Krahn M D; Moore M J; Tannock I F

CS Department of Medical Oncology and Hematology, Princess Margaret Hospital, University of Toronto, Toronto, British Columbia.

SO Journal of urology, **(2000 May)** 163 (5) 1481-5.
Journal code: 0376374. ISSN: 0022-5347.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Abridged Index Medicus Journals; Priority Journals

EM 200005

ED Entered STN: 20000512
Last Updated on STN: 20000512
Entered Medline: 20000502

AB PURPOSE: We determine prostate specific antigen (PSA) response and durability, and prognostic factors associated with response and survival in patients with symptomatic hormone refractory prostate cancer treated with mitoxantrone and **prednisone** at a single institution. We then compare the results with those of a randomized phase III clinical trial. MATERIALS AND METHODS: A retrospective review of all 133 patients treated with mitoxantrone and **prednisone** at Princess Margaret Hospital since 1994 was performed. PSA response and duration, and overall survival were determined as well as the influence of baseline factors on these outcome parameters. Results were compared to those for patients randomized to receive mitoxantrone and **prednisone** in the Canadian clinical trial which demonstrated palliative benefit of this regimen. RESULTS: Patients treated after trial closure had shorter survival ($p = 0.003$) but represented a poorer prognosis cohort. PSA

response of the trial and post-trial cases was 34% and 28%, respectively (p = 0.36), and median duration of response was 118 and 175 days or greater, respectively. Factors predictive of PSA response in the non-trial cohort were longer time from diagnosis of prostate cancer (p = 0. 027) and higher baseline PSA (p = 0.013). Factors predictive of increased survival in both groups were younger age (p <0.04), better baseline Eastern Cooperative Oncology Group performance status (p <0. 02), and higher hemoglobin (p </=0.05) and PSA response (p <0.0001). Gleason score was not predictive of response or survival. CONCLUSIONS: Although patients treated outside of the trial had poorer prognostic features, rates of PSA response to mitoxantrone and **prednisone** were comparable. Factors predictive of survival were similar in the 2 cohorts. Results of the randomized trial are generalizable to clinical practice.

CT Check Tags: Comparative Study; Human; Male; Support, Non-U.S. Gov't
*Adenocarcinoma: BL, blood
*Adenocarcinoma: DT, drug therapy
Adenocarcinoma: MO, mortality
Aged
*Antineoplastic Combined Chemotherapy Protocols: TU, therapeutic use
Clinical Trials, Phase III
Middle Aged
Mitoxantrone: AD, administration & dosage
Multicenter Studies
Prednisone: AD, administration & dosage
Prognosis
*Prostate-Specific Antigen: BL, blood
*Prostatic Neoplasms: BL, blood
***Prostatic Neoplasms: DT, drug therapy**
Prostatic Neoplasms: MO, mortality
Randomized Controlled Trials
Retrospective Studies
Survival Rate

RN **53-03-2 (Prednisone)**; 65271-80-9 (Mitoxantrone)
CN 0 (Antineoplastic Combined Chemotherapy Protocols); EC 3.4.21.77 (Prostate-Specific Antigen)

L139 ANSWER 5 OF 61 MEDLINE on STN
AN 2000067760 MEDLINE
DN PubMed ID: 10604271
TI Docetaxel (Taxotere) and estramustine versus mitoxantrone and **prednisone** for hormone-refractory prostate cancer: scientific basis and design of Southwest Oncology Group Study 9916.
AU Hussain M; Petrylak D; Fisher E; Tangen C; Crawford D
CS Department of Internal Medicine, Wayne State University School of Medicine and Barbara Ann Karmanos Cancer Institute, Detroit, MI, USA.
SO Seminars in oncology, **(1999 Oct)** 26 (5 Suppl 17) 55-60.
Journal code: 0420432. ISSN: 0093-7754.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199912
ED Entered STN: 20000113
Last Updated on STN: 20000113
Entered Medline: 19991222
AB Hormone-refractory prostate cancer is the terminal step in the natural history of prostate cancer. To date, no chemotherapeutic agents have been shown to impact clinical outcome at this stage. Recently, the Food and Drug Administration approved the combination of mitoxantrone and **prednisone** based solely on its superior palliative effects as

compared to steroids alone in 2 randomized trials. Progress in biologically driven drug development has led to the identification of several estramustine-based regimens that, although based on single institution experience, appear to have at least a comparable but very promising level of activity in hormone-refractory prostate cancer patients. One such combination, estramustine plus docetaxel (Taxotere; Rhone-Poulenc Rorer, Collegeville, PA), is particularly attractive because of its convenient schedule and side effect profile. To objectively assess the therapeutic benefit of this combination, the Southwest Oncology Group is initiating a randomized phase III trial comparing estramustine and docetaxel with the standard arm of mitoxantrone and **prednisone** using time to progression and survival as the primary end points. Secondary end points will include toxicity profiles, assessments of quality of life parameters, and magnitude of decline of prostate-specific antigen levels between the two treatment arms.

CT Check Tags: Comparative Study; Human; Male
*Adenocarcinoma: DT, drug therapy
Adenocarcinoma: SC, secondary
*Antineoplastic Combined Chemotherapy Protocols: TU, therapeutic use
Clinical Trials, Phase III
Estramustine: AD, administration & dosage
Mitoxantrone: AD, administration & dosage
*Neoplasms, Hormone-Dependent: DT, drug therapy
Neoplasms, Hormone-Dependent: PA, pathology
Paclitaxel: AD, administration & dosage
*Paclitaxel: AA, analogs & derivatives
Prednisone: AD, administration & dosage
***Prostatic Neoplasms: DT, drug therapy**
Prostatic Neoplasms: PA, pathology
Randomized Controlled Trials
*Taxoids

RN 114977-28-5 (docetaxel); 2998-57-4 (Estramustine); 33069-62-4 (Paclitaxel); **53-03-2 (Prednisone)**; 65271-80-9 (Mitoxantrone)

CN 0 (Antineoplastic Combined Chemotherapy Protocols); 0 (Taxoids)

=> d all l140 1-3

L140 ANSWER 1 OF 22 MEDLINE on STN
AN 2001154998 MEDLINE
DN PubMed ID: 11204256
TI Suramin administration is associated with a decrease in serum calcium levels.
AU Walther M M; Rehak N N; Venzon D; Myers C E; Linehan W M; Figg W D
CS Urologic Oncology Branch, DCS/NCI/NIH, Bethesda, MD 20892-1501, USA.. macw@nih.gov
SO World journal of urology, **(2000 Dec)** 18 (6) 388-91.
Journal code: 8307716. ISSN: 0724-4983.
CY Germany: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200103
ED Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010322
AB Suramin has been shown to have an effect on bone resorption in in vitro models. It is not clear if a similar effect is seen in patients treated with suramin. The clinical effect of suramin treatment on total serum calcium was examined in two groups of patients with hormone-refractory

prostate cancer. In all, 28 patients in group 1 were examined within 2 weeks before and 2 weeks after suramin treatment and 72 patients in group 2 were examined within 2 weeks before, during, and after treatment with suramin. In addition, calcium controls spiked with suramin were run in three different commercially available assays for evaluation of the effect of suramin dose on calcium determination. Group 1 patients showed a decrease in serum calcium after treatment with suramin. The mean uncorrected serum calcium level was 2.29 +/- 0.025 mmol/l before treatment and 2.09 +/- 0.025 mmol/l after treatment ($P < 0.0001$, paired Wilcoxon test). The mean serum calcium value corrected for albumin was 2.33 +/- 0.02 mmol/l before treatment and 2.24 +/- 0.02 mmol/l after treatment ($P = 0.0022$, paired Wilcoxon test). Group 2 patients also displayed a decrease in serum calcium after treatment with suramin. The mean baseline value was 2.23 mmol/l (median 2.26 mmol/l, range 1.20-2.54 mmol/l). The mean level of serum calcium corrected for albumin as determined at the end of treatment was 2.14 mmol/l (median 2.16 mmol/l, range 0.98 2.46 mmol/l). In all, 48 patients for whom pre- and post-treatment values were available for analysis displayed a median calcium decrease of 0.09 mmol/l ($P = 0.0005$, Wilcoxon signed-rank test for the null hypothesis of no change). For 68 patients in group 2, data on serial serum calcium measurements during treatment were available for analysis. A projected median decrease in serum calcium of 0.06 mmol/l (range 0.43 to 0.72 mmol/l) over an 8-week interval of suramin therapy was found. Overall, 47 of the 68 slopes were negative ($P = 0.0022$, Wilcoxon signed-rank test). Nine patients were treated with suramin for less than 6 weeks. These patients' calcium levels were significantly higher than those of 50 patients treated for longer periods (median value 2.24 versus 2.16 mmol/l, $P = 0.035$, Wilcoxon rank-sum test). No correlation was found between suramin dose and calcium level using the Kodak Ektachem, Hitachi 914, or Synchron Clinical System CX3 method. In conclusion, suramin treatment was consistently associated with decreases in serum calcium in two groups of patients with hormone-refractory cancer. Suramin placed in calcium controls did not affect calcium determination using three commercially available methods.

CT Check Tags: Human; Male
Anti-Inflammatory Agents: TU, therapeutic use
Antineoplastic Agents: AD, administration & dosage
*Antineoplastic Agents: TU, therapeutic use
Antineoplastic Agents, Hormonal: TU, therapeutic use
Antineoplastic Combined Chemotherapy Protocols
*Calcium: BL, blood
Drug Administration Schedule
Drug Resistance
Hormones: TU, therapeutic use
Hydrocortisone: TU, therapeutic use
Leuprolide: TU, therapeutic use
Pilot Projects
*Prostatic Neoplasms: BL, blood
***Prostatic Neoplasms: DT, drug therapy**
Retreatment
Retrospective Studies
Suramin: AD, administration & dosage
*Suramin: TU, therapeutic use

RN 145-63-1 (Suramin); 50-23-7 (Hydrocortisone); 53714-56-0 (Leuprolide); 7440-70-2 (Calcium)

CN 0 (Anti-Inflammatory Agents); 0 (Antineoplastic Agents); 0 (Antineoplastic Agents, Hormonal); 0 (Antineoplastic Combined Chemotherapy Protocols); 0 (Hormones)

L140 ANSWER 2 OF 22 MEDLINE on STN

AN 2000385998 MEDLINE

DN PubMed ID: 10848697
TI Stilboestrol plus adrenal suppression as salvage treatment for patients failing treatment with luteinizing hormone-releasing hormone analogues and orchidectomy.
AU Farrugia D; Ansell W; Singh M; Philp T; Chinegwundoh F; Oliver R T
CS Urological Oncology, The Royal Hospitals Trust, and Whipps Cross Hospital, London, UK.
SO BJU international, **(2000 Jun)** 85 (9) 1069-73.
Journal code: 100886721. ISSN: 1464-4096.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200008
ED Entered STN: 20000818
Last Updated on STN: 20000818
Entered Medline: 20000810
AB OBJECTIVE: To investigate the efficacy of low-dose stilboestrol (SB) with hydrocortisone in patients with advanced prostate cancer refractory to androgen suppression. PATIENTS AND METHODS: Thirty-four consecutive patients (median age 70 years, range 51-83) with metastatic disease who progressed on hormone therapy, as shown by recurrent/worsening symptoms and an increase in prostate-specific antigen (PSA) level, were recruited and discontinued hormonal treatment before starting SB. Patients received SB (1 mg/day) combined with hydrocortisone (40 mg/day). In an attempt to reduce the incidence of thrombo-embolic events, aspirin (75 mg/day) was also added. RESULTS: Stilboestrol was the second-line treatment in 19 patients and the third or fourth in 15. The median (range) duration of treatment with SB was 5 (0.5-21) months and the median follow-up 7.5 months, with 18 patients still alive and 14 still on treatment. Of 29 symptomatic patients, 24 had symptomatic improvement and five had no clear benefit; the median duration of benefit was 6 (2-21) months. The PSA level decreased by 0-50% in six patients, by 50-90% in 13 and by > 90% in eight, while there was symptomatic improvement in these three categories in five, 11 and seven patients, respectively. The median times to PSA nadir and progression were 4 and 6 months, respectively. Some thrombo-embolic events and fluid retention occurred but overall the treatment was well tolerated. CONCLUSION: Low-dose SB with hydrocortisone is effective in refractory prostate cancer, although there is some toxicity. Randomized studies against hydrocortisone or SB alone are needed to establish the cost/benefit ratio of this combination.
CT Check Tags: Human; Male
Aged
Aged, 80 and over
*Antineoplastic Agents, Hormonal: TU, therapeutic use
Aspirin: TU, therapeutic use
*Diethylstilbestrol: TU, therapeutic use
Drug Therapy, Combination
Gonadorelin: AA, analogs & derivatives
Gonadorelin: AI, antagonists & inhibitors
***Hydrocortisone: TU, therapeutic use**
Middle Aged
*Orchiectomy: MT, methods
***Prostatic Neoplasms: DT, drug therapy**
Salvage Therapy: MT, methods
Treatment Failure
RN 33515-09-2 (Gonadorelin); 50-23-7 (Hydrocortisone); 50-78-2 (Aspirin); 56-53-1 (Diethylstilbestrol)
CN 0 (Antineoplastic Agents, Hormonal)

L140 ANSWER 3 OF 22 MEDLINE on STN
AN 2000200496 MEDLINE
DN PubMed ID: 10735891
TI Suramin therapy for patients with symptomatic hormone-refractory prostate cancer: results of a randomized phase III trial comparing suramin plus hydrocortisone to placebo plus hydrocortisone.
AU Small E J; Meyer M; Marshall M E; Reyno L M; Meyers F J; Natale R B; Lenehan P F; Chen L; Slichenmyer W J; Eisenberger M
CS University of California at San Francisco Comprehensive Cancer Center, San Francisco 94115, USA.. smalle@medicine.ucsf.du
SO Journal of clinical oncology : official journal of the American Society of Clinical Oncology, **(2000 Apr)** 18 (7) 1440-50.
Journal code: 8309333. ISSN: 0732-183X.
CY United States
DT (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE III)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LA English
FS Priority Journals
EM 200004
ED Entered STN: 20000505
Last Updated on STN: 20000505
Entered Medline: 20000421
AB PURPOSE: Suramin is a novel agent that has demonstrated preliminary evidence of antitumor activity in hormone-refractory prostate cancer (HRPC). A prospective randomized clinical trial was designed to evaluate pain and opioid analgesic intake as surrogates for antitumor response in HRPC patients with significant, opioid analgesic-dependent pain. PATIENTS AND METHODS: A double-blind, placebo-controlled trial randomized patients to receive a 78-day, outpatient regimen of either suramin plus hydrocortisone (HC, 40 mg/d) or placebo plus HC. Treatment assignment was unblinded when either disease progression or dose-limiting toxicity occurred; placebo patients were allowed to cross-over to open-label suramin plus HC. In addition to pain and opioid analgesic intake, prostate-specific antigen (PSA) response, time to disease progression, quality of life, performance status, and survival were compared. RESULTS: Overall mean reductions in combined pain and opioid analgesic intake were greater for suramin plus HC (rank sum P =.0001). Pain response was achieved in a higher proportion of patients receiving suramin than placebo (43% v 28%; P =.001), and duration of response was longer for suramin responders (median, 240 v 69 days; P =.0027). Time to disease progression was longer (relative risk = 1.5; 95% confidence interval, 1.2 to 1.9) and the proportion of patients with a greater than 50% decline in PSA was higher (33% v 16%; P =.01) in patients who received suramin. Neither quality of life nor performance status was decreased by suramin treatment, and overall survival was similar. Most adverse events were of mild or moderate intensity and were easily managed medically. CONCLUSION: Outpatient treatment with suramin plus HC is well tolerated and provides moderate palliative benefit and delay in disease progression for patients with symptomatic HRPC.
CT Check Tags: Human; Male; Support, Non-U.S. Gov't
Adult
Aged
Aged, 80 and over
Anti-Inflammatory Agents, Non-Steroidal: AD, administration & dosage
*Anti-Inflammatory Agents, Non-Steroidal: TU, therapeutic use
Antineoplastic Agents: AD, administration & dosage
*Antineoplastic Agents: TU, therapeutic use
Disease Progression

Double-Blind Method
Drug Therapy, Combination
Hydrocortisone: AD, administration & dosage
***Hydrocortisone: TU, therapeutic use**
Middle Aged
*Pain: DT, drug therapy
*Palliative Care
***Prostatic Neoplasms: DT, drug therapy**
Prostatic Neoplasms: PA, pathology
Prostatic Neoplasms: PP, physiopathology
Quality of Life
Suramin: AD, administration & dosage
*Suramin: TU, therapeutic use
Treatment Outcome
RN 145-63-1 (Suramin); 50-23-7 (Hydrocortisone)
CN 0 (Anti-Inflammatory Agents, Non-Steroidal); 0 (Antineoplastic Agents)

=> d all l141 1 2 4

L141 ANSWER 1 OF 56 MEDLINE on STN
AN 2000468935 MEDLINE
DN PubMed ID: 11022738
TI Inhibitors of the key enzymes of androgen synthesis: potential agents as targets for prostate cancer.
AU Takeda M; Hosaka M
CS Department of Urology, Yokohama City University School of Medicine.
SO Nippon rinsho. Japanese journal of clinical medicine, **(2000 Jul)** 58 Suppl 312-6. Ref: 14
Journal code: 0420546. ISSN: 0047-1852.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW LITERATURE)
LA Japanese
FS Priority Journals
EM 200012
ED Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001212
CT Check Tags: Human; Male
17-Hydroxysteroid Dehydrogenases: AI, antagonists & inhibitors
*Androgen Antagonists: TU, therapeutic use
*Androstenols: TU, therapeutic use
Animals
*Antineoplastic Agents, Hormonal: TU, therapeutic use
*Carbazoles: TU, therapeutic use
Enzyme Inhibitors: TU, therapeutic use
*Imidazoles: TU, therapeutic use
***Ketoconazole: TU, therapeutic use**
***Prostatic Neoplasms: DT, drug therapy**
Steroid 17-alpha-Hydroxylase: AI, antagonists & inhibitors
*Testosterone: BI, biosynthesis
RN 115575-11-6 (liarozole); 154229-19-3 (abiraterone); 58-22-0 (Testosterone); 65277-42-1 (Ketoconazole)
CN 0 (Androgen Antagonists); 0 (Androstenols); 0 (Antineoplastic Agents, Hormonal); 0 (Carbazoles); 0 (Enzyme Inhibitors); 0 (Imidazoles); 0 (YM 116); EC 1.1.- (17-Hydroxysteroid Dehydrogenases); EC 1.14.99.9 (Steroid 17-alpha-Hydroxylase)

L141 ANSWER 2 OF 56 MEDLINE on STN
AN 2000434743 MEDLINE
DN PubMed ID: 10564905
TI Treating prostate cancer. Part V: androgen deprivation and chemotherapy.
AU Anonymous
SO Harvard men's health watch, **(1999 Dec)** 4 (5) 5-8. Ref: 0
Journal code: 9802701. ISSN: 1089-1102.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Consumer Health
EM 200009
ED Entered STN: 20000928
Last Updated on STN: 20000928
Entered Medline: 20000921
CT Check Tags: Human; Male
*Androgen Antagonists: TU, therapeutic use
Estrogens: TU, therapeutic use
Gonadorelin: AG, agonists
Ketoconazole: TU, therapeutic use
Orchiectomy
***Prostatic Neoplasms: DT, drug therapy**
Prostatic Neoplasms: SU, surgery
RN 33515-09-2 (Gonadorelin); 65277-42-1 (Ketoconazole)
CN 0 (Androgen Antagonists); 0 (Estrogens)

L141 ANSWER 4 OF 56 MEDLINE on STN
AN 2000150750 MEDLINE
DN PubMed ID: 10688042
TI Efficacy of microtubule-active drugs followed by ketoconazole in human metastatic prostate cancer cell lines.
AU Blagosklonny M V; Dixon S C; Figg W D
CS Medicine Branch, Division of Clinical Sciences, National Cancer Institute, NIH, Bethesda, Maryland 20892, USA.
SO Journal of urology, **(2000 Mar)** 163 (3) 1022-6.
Journal code: 0376374. ISSN: 0022-5347.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 200003
ED Entered STN: 20000327
Last Updated on STN: 20000327
Entered Medline: 20000316
AB PURPOSE: Once a relapse occurs following primary endocrine treatment, metastatic prostate cancer is one of the most therapy-resistant human neoplasms. Ketoconazole is used for complete androgen deprivation, and recent data suggest it has direct activity against prostate cancer cells. MATERIALS AND METHODS: LNCaP, DU145, and PC3 cells, human prostate cancer cell lines, and HL60, a human leukemia cell line, were lysed and soluble proteins were harvested. Cells were plated in 96-well flat bottom plates and then exposed to the pharmacological agents, ketoconazole, vinblastine and paclitaxel. DNA synthesis was monitored by 3H-thymidine incorporation. RESULTS: We demonstrate that ketoconazole exerts a cytostatic effect on a panel of human prostate cancer cell lines, with IC50 of 4 to 5 microg./ml., 12 microg./ml., and 25 microg./ml. for LNCaP, PC3/PC3M, and DU145 cells, respectively. On the other hand, using microtubule-active drugs, vinblastine and paclitaxel, we found that PC3M

and PC3 cells were more resistant than either DU145 or LNCaP cells. This resistance was associated with a lesser degree of Raf-1 and Bcl-2 phosphorylation following exposure to microtubule-active drugs. Combinations of microtubule-active drugs with ketoconazole were a beneficial treatment in DU145 cancer cells. Furthermore, ketoconazole blocked recovery of all the prostate cancer cell lines following 24 hours-pulse treatment with vinblastine. CONCLUSION: Pulse-administration of vinblastine followed by continuous administration of ketoconazole warrants investigation in the treatment of hormone-independent metastatic prostate cancer.

CT Check Tags: Human; Male
*Antineoplastic Agents: TU, therapeutic use
Drug Screening Assays, Antitumor
***Ketoconazole: TU, therapeutic use**
Microtubules: DE, drug effects
*Paclitaxel: TU, therapeutic use
Phosphorylation: DE, drug effects
***Prostatic Neoplasms: DT, drug therapy**
*Prostatic Neoplasms: SC, secondary
Tumor Cells, Cultured
*Vinblastine: TU, therapeutic use
RN 33069-62-4 (Paclitaxel); 65277-42-1 (Ketoconazole); 865-21-4 (Vinblastine)
CN 0 (Antineoplastic Agents)

=> d all l142 1 2 4

L142 ANSWER 1 OF 45 MEDLINE on STN
AN 2000512716 MEDLINE
DN PubMed ID: 11071217
TI Androgen blockade in prostate cancer.
CM Comment on: Lancet. 2000 Apr 29;355(9214):1491-8. PubMed ID: 10801170
AU Labrie F; Candas B
SO Lancet, **(2000 Jul 22)** 356 (9226) 341-2.
Journal code: 2985213R. ISSN: 0140-6736.
CY ENGLAND: United Kingdom
DT Commentary
Letter
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 200011
ED Entered STN: 20010322
Last Updated on STN: 20011004
Entered Medline: 20001128
CT Check Tags: Human; Male
*Androgen Antagonists: TU, therapeutic use
Cyproterone Acetate: TU, therapeutic use
*Flutamide: TU, therapeutic use
*Imidazoles: TU, therapeutic use
Meta-Analysis
Orchiectomy
***Prostatic Neoplasms: DT, drug therapy**
RN 13311-84-7 (Flutamide); 427-51-0 (Cyproterone Acetate); 63612-50-0 (nilutamide)
CN 0 (Androgen Antagonists); 0 (Imidazoles)

L142 ANSWER 2 OF 45 MEDLINE on STN
AN 2000511502 MEDLINE
DN PubMed ID: 11062379
TI Neoadjuvant hormone therapy: the Canadian trials.

AU Klotz L; Gleave M; Goldenberg S L
CS Sunnybrook Health Science Center, University of Toronto, Toronto, Ontario, Canada.. Laurence.klotz@utoronto.ca
SO Molecular urology, **(2000 Fall)** 4 (3) 233-7;discussion 239. Ref: 10
Journal code: 9709255. ISSN: 1091-5362.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200012
ED Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001207
AB The Canadian Urologic Oncology Group has carried out three studies of neoadjuvant hormonal therapy (NHT) in prostate cancer. The first, a study of 3 months of cyproterone acetate (CPA) 100 mg TID in patients undergoing external-beam radiation therapy, showed a benefit with respect to time to biochemical progression. There are no survival or clinical progression data available from this study. The second study involved 3 months of CPA prior to radical prostatectomy compared with radical prostatectomy alone and enrolled 200 patients. The probability of biochemical progression at 36 months was similar in the two groups (CPA 40%; surgery alone 30%; P = 0.3233). More recently, we have carried out a randomized trial of 3 v 8 months of leuprolide plus flutamide prior to radical prostatectomy in 547 patients. Patients were stratified by clinical stage, Gleason grade, and serum prostate specific antigen (PSA) concentration. In the 3- and 8-month groups, presurgery PSA concentrations were <0.1 ng/mL in 35% v 73%, and >0.3 ng/mL in 37% v 10%, respectively. In the 3- and 8-month groups, the positive margin rates were 17% and 5% and the organ-confined rates 71% and 91% (P < 0.01). One-year follow-up is now available on the entire cohort. Data regarding time to biochemical and clinical progression and overall and disease-specific survival will be required to determine whether this change in the pathologic findings translates into a patient benefit.
CT Check Tags: Human; Male
*Androgen Antagonists: TU, therapeutic use
*Antineoplastic Agents, Hormonal: TU, therapeutic use
Antineoplastic Combined Chemotherapy Protocols: TU, therapeutic use
Canada
Cyproterone Acetate: TU, therapeutic use
Disease Progression
Flutamide: TU, therapeutic use
Leuprolide: TU, therapeutic use
Neoadjuvant Therapy
Prostate-Specific Antigen: BL, blood
Prostatectomy
***Prostatic Neoplasms: DT, drug therapy**
Prostatic Neoplasms: PA, pathology
Prostatic Neoplasms: TH, therapy
Randomized Controlled Trials
Survival Rate
RN 13311-84-7 (Flutamide); 427-51-0 (Cyproterone Acetate); 53714-56-0 (Leuprolide)
CN 0 (Androgen Antagonists); 0 (Antineoplastic Agents, Hormonal); 0 (Antineoplastic Combined Chemotherapy Protocols); EC 3.4.21.77 (Prostate-Specific Antigen)

L142 ANSWER 4 OF 45 MEDLINE on STN
AN 2000394289 MEDLINE
DN PubMed ID: 10925096
TI Long-term neoadjuvant hormone therapy prior to radical prostatectomy: evaluation of risk for biochemical recurrence at 5-year follow-up.
AU Gleave M E; La Bianca S E; Goldenberg S L; Jones E C; Bruchovsky N; Sullivan L D
CS Division of Urology, University of British Columbia, Vancouver General Hospital, Vancouver, British Columbia, Canada.
SO Urology, **(2000 Aug 1)** 56 (2) 289-94.
Journal code: 0366151. ISSN: 1527-9995.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200008
ED Entered STN: 20000824
Last Updated on STN: 20010521
Entered Medline: 20000814
AB OBJECTIVES: To assess the effects of 8 months of neoadjuvant therapy on pathologic stage and biochemical recurrence rates. METHODS: One hundred fifty-six men with clinically localized prostate cancer were treated with neoadjuvant combined androgen withdrawal therapy for 8 months prior to radical prostatectomy. Preoperative clinical stage, Gleason score, and serum prostate-specific antigen (PSA) levels were compared with treatment outcome (pathologic stage and PSA recurrence). RESULTS: PSA at diagnosis was 10 microg/L or higher in 36% with a mean of 11.5 microg/L. Clinical stage was T1c in 18%, T2 in 74%, and T3a in 8%. Gleason score was 6 or lower in 76% and 7 or higher in 24%. Pathologic stage was T0 in 13%, T2 in 66%, T3 (specimen confined) in 13%, T3 (margin positive) in 6%, and TxN+ in 2%. Incidence of positive margins increased with clinical stage T3a versus organ-confined disease (25% versus 4%, P <0.05), pretreatment Gleason scores 7 or higher versus Gleason scores 6 or lower (11% versus 4%, P = NS), and pretreatment PSA levels higher than 10 microg/L compared with PSA levels lower than 10 microg/L (15% versus 0%, P <0.01). Overall PSA recurrence rate was 12.2% after a mean postoperative follow-up of 54 months. Risk of PSA recurrence increased with clinical stage (25% T3 versus 11% organ confined, P <0.01), pretreatment PSA (7% if PSA lower than 10 microg/L versus 21% if 10 microg/L or higher, P <0.02), Gleason score (9% if 6 or lower versus 22% if 7 or higher, P <0.02), and pathologic stage (6% of pT2, 24% of pT3M-, and 56% of pT3M+, P <0.01). PSA recurrences occurred in 6% of patients with no adverse preoperative risk factors, 12% with any one of the high-risk factors, and 29% with any two of the high-risk factors. CONCLUSIONS: Risk of PSA recurrence after 8 months of neoadjuvant therapy is low after 5 years of follow-up and remains proportional to the presence of adverse preoperative risk factors. Prospective randomized studies are required to determine whether longer duration of neoadjuvant therapy reduces the risk of biochemical recurrence after radical prostatectomy.
CT Check Tags: Human; Male
Adult
Aged
*Androgen Antagonists: TU, therapeutic use
*Antineoplastic Agents, Hormonal: TU, therapeutic use
Combined Modality Therapy
Cyproterone Acetate: TU, therapeutic use
Diethylstilbestrol: TU, therapeutic use
Drug Therapy, Combination
Flutamide: TU, therapeutic use
Follow-Up Studies

Leuprolide: TU, therapeutic use
Lymph Node Excision
Middle Aged
*Neoadjuvant Therapy
Postoperative Complications: EP, epidemiology
*Prostatectomy
Prostatic Neoplasms: DI, diagnosis
***Prostatic Neoplasms: DT, drug therapy**
*Prostatic Neoplasms: SU, surgery
Recurrence
Treatment Outcome
RN 13311-84-7 (Flutamide); 427-51-0 (Cyproterone Acetate); 53714-56-0 (Leuprolide); 56-53-1 (Diethylstilbestrol)
CN 0 (Androgen Antagonists); 0 (Antineoplastic Agents, Hormonal)

=> d all l143 1 2 5

L143 ANSWER 1 OF 293 MEDLINE on STN
AN 2002005232 MEDLINE
DN PubMed ID: 11194670
TI [Radical prostatectomy with broadened scope of indications - analysis of early experience].
Radikalna prostatektomiia s razshireni pokazaniia - nachalen opit.
AU Chakarov S; Bechev R; Lazarov Z; Fachikov Ts; Rangelov S
CS Government University Hospital "St Anna," Urologic Clinic, Medical University, Sofia, Bulgaria.
SO Khirurgiia, **(1999)** 55 (3) 47-8.
Journal code: 0376355. ISSN: 0450-2167.
CY Bulgaria
DT Journal; Article; (JOURNAL ARTICLE)
LA Bulgarian
FS Priority Journals
EM 200201
ED Entered STN: 20020121
Last Updated on STN: 20020128
Entered Medline: 20020123
CT Check Tags: Human; Male
Acid Phosphatase: AN, analysis
Acid Phosphatase: BL, blood
Aged
Androgen Antagonists: TU, therapeutic use
Antineoplastic Agents, Hormonal: TU, therapeutic use
Biopsy
Flutamide: TU, therapeutic use
Goserelin: TU, therapeutic use
Middle Aged
Prostate-Specific Antigen: BL, blood
*Prostatectomy: MT, methods
Prostatic Neoplasms: DI, diagnosis
Prostatic Neoplasms: DT, drug therapy
Prostatic Neoplasms: SC, secondary
*Prostatic Neoplasms: SU, surgery
RN 13311-84-7 (Flutamide); 65807-02-5 (Goserelin)
CN 0 (Androgen Antagonists); 0 (Antineoplastic Agents, Hormonal); EC 3.1.3.2 (Acid Phosphatase); EC 3.4.21.77 (Prostate-Specific Antigen)

L143 ANSWER 2 OF 293 MEDLINE on STN
AN 2001353116 MEDLINE
DN PubMed ID: 11114872

TI Neoadjuvant hormone therapy and radical radiotherapy for localized prostate cancer: poorer biochemical outcome using flutamide alone.
AU Wilson K S; Ludgate C M; Wilson A G; Alexander A S
CS University of British Columbia, Vancouver, BC, Canada.
SO Canadian journal of urology, **(2000 Oct)** 7 (5) 1099-103.
Journal code: 9515842. ISSN: 1195-9479.
CY Canada
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200106
ED Entered STN: 20010625
Last Updated on STN: 20010625
Entered Medline: 20010621
AB Since a recent meta-analysis of non-steroidal anti-androgen therapy in metastatic prostate cancer concluded that survival was worse compared with medical or surgical androgen withdrawal, we analyzed our experience with flutamide monotherapy and other forms of neoadjuvant hormone therapy (NHT) prior to radiation therapy in clinically localized prostate cancer. A total of 45 patients received flutamide and 328 patients received other NHT. Flutamide patients had higher PSA levels at diagnosis and shorter duration of treatment, which could bias the results against flutamide monotherapy. Kaplan Meier analysis of PSA -- disease free survival showed significantly poorer outcome with flutamide monotherapy. Multivariate analysis supported this conclusion. Until equivalence to other forms of NHT is shown, we do not recommend flutamide monotherapy prior to radical radiation. A prospective randomized trial would be necessary to confirm this conclusion.
CT Check Tags: Comparative Study; Human; Male; Support, Non-U.S. Gov't
*Adenocarcinoma: DT, drug therapy
Adenocarcinoma: PA, pathology
*Adenocarcinoma: RT, radiotherapy
*Androgen Antagonists: TU, therapeutic use
*Antineoplastic Agents, Hormonal: TU, therapeutic use
Chi-Square Distribution
***Flutamide: TU, therapeutic use**
Multivariate Analysis
Neoadjuvant Therapy
Neoplasm Staging
Prostate-Specific Antigen: BL, blood
***Prostatic Neoplasms: DT, drug therapy**
Prostatic Neoplasms: PA, pathology
*Prostatic Neoplasms: RT, radiotherapy
Radiotherapy Dosage
Regression Analysis
RN 13311-84-7 (Flutamide)
CN 0 (Androgen Antagonists); 0 (Antineoplastic Agents, Hormonal); EC 3.4.21.77 (Prostate-Specific Antigen)

L143 ANSWER 5 OF 293 MEDLINE on STN
AN 2001043137 MEDLINE
DN PubMed ID: 11095136
TI A prospective randomized multicenter study of chlormadinone acetate versus flutamide in total androgen blockade for prostate cancer.
AU Ozono S; Okajima E; Yamaguchi A; Yoshikawa M; Iwai A; Moriya A; Yoshida K; Samma S; Maruyama Y; Hirao Y
CS Department of Urology, Nara Medical University, Kashihara, Japan.. ozn-kkr@nmu-gw.naramed-u.ac.jp
SO Japanese journal of clinical oncology, **(2000 Sep)** 30 (9) 389-96.
Journal code: 0313225. ISSN: 0368-2811.

CY Japan
DT (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
(RANDOMIZED CONTROLLED TRIAL)
LA English
FS Priority Journals
EM 200012
ED Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001207
AB BACKGROUND: A randomized multicenter study was conducted to investigate the efficacy of total androgen blockade (TAB) for patients with previously untreated prostate cancer using the steroidal anti-androgen chlormadinone acetate (CMA) and the non-steroidal anti-androgen flutamide. We also compared the liver dysfunction in these two arms. METHODS: From November 1995 to October 1997, 71 patients were registered into this study and 70 of them were eligible. RESULTS: There was no significant difference in the efficacy of TAB between CMA and flutamide at 24 weeks. The testosterone and prostate-specific antigen (PSA) levels in patients administered flutamide (Group II) increased significantly 3 days after the first dose of LH-RH analog, whereas no such increase was observed in patients administered CMA (Group I), indicating that CMA prevented the flare-up. Parameters of liver function, serum GOT and GPT levels, which were normal at the baseline, became abnormal in 30.0% and 35.3%, respectively, of patients in Group II. These figures were significantly higher than the corresponding figures of 6.3% and 12.5%, respectively, in Group I. When the degree of change in each of these parameters was analyzed, both GOT and GPT levels showed a significantly greater increase in Group II than in Group I. CONCLUSION: These results indicate that attention must be paid to changes in liver function during the administration of flutamide in patients with prostate cancer even if their baseline liver function is normal. It is also suggested that CMA may be better tolerated from the viewpoint of the drug effects on liver function.
CT Check Tags: Human; Male
*Adenocarcinoma: DT, drug therapy
Adenocarcinoma: PP, physiopathology
Aged
*Androgen Antagonists: TU, therapeutic use
*Antineoplastic Agents, Hormonal: TU, therapeutic use
*Chlormadinone Acetate: AA, analogs & derivatives
*Chlormadinone Acetate: TU, therapeutic use
*Enzyme Inhibitors: TU, therapeutic use
***Flutamide: TU, therapeutic use**
Liver: PP, physiopathology
Prospective Studies
***Prostatic Neoplasms: DT, drug therapy**
Prostatic Neoplasms: PP, physiopathology
RN 13311-84-7 (Flutamide); 302-22-7 (Chlormadinone Acetate); 3114-44-1 (chlormadinol acetate)
CN 0 (Androgen Antagonists); 0 (Antineoplastic Agents, Hormonal); 0 (Enzyme Inhibitors)

=> d all l144 1-3

L144 ANSWER 1 OF 17 MEDLINE on STN
AN 2000476033 MEDLINE
DN PubMed ID: 11026565
TI 1,25-Dihydroxyvitamin D3 decreases human prostate cancer cell adhesion and

migration.
AU Sung V; Feldman D
CS Department of Medicine, Stanford University School of Medicine, CA 94305-5103, USA.
NC DK42482 (NIDDK)
T32 DK07217 (NIDDK)
SO Molecular and cellular endocrinology, **(2000 Jun)** 164 (1-2) 133-43.
Journal code: 7500844. ISSN: 0303-7207.
CY Ireland
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200102
ED Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010208
AB 1,25-Dihydroxyvitamin-D3 [1,25(OH)2D3], the active hormonal metabolite of vitamin D, acts through a specific nuclear receptor to inhibit proliferation and promote differentiation of several tumor cell types including the LNCaP, DU145 and PC-3 prostate cancer cell lines as well as primary prostate tumor lines. 1,25(OH)2D3 can also decrease invasion of breast and prostate cancer cell lines in vitro. We confirm this latter finding in the DU145 and PC-3 prostate cancer cell lines, and further show that 1,25(OH)2D3 inhibits overall invasion, cell adhesion and migration to the basement membrane matrix protein laminin. These changes appear to be due in part to a 1,25(OH)2D3-induced decrease in expression of alpha6 and beta4 integrins, both of which are receptors for laminin and associated with increased migration and invasion of prostate cancer cells in vitro. Blocking function of these particular integrins with antibodies inhibits both adhesion and migration of the cells. Collectively, these data demonstrate that 1,25(OH)2D3, in addition to decreasing proliferation of tumor cells, can also inhibit prostate cancer cell invasion through modulation of select cell surface adhesion molecules.
CT Check Tags: Human; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, Non-P.H.S.; Support, U.S. Gov't, P.H.S.
*Calcitriol: PD, pharmacology
Calcitriol: TU, therapeutic use
*Calcium Channel Agonists: PD, pharmacology
Calcium Channel Agonists: TU, therapeutic use
Cell Adhesion: DE, drug effects
*Cell Movement: DE, drug effects
***Prostatic Neoplasms: DT, drug therapy**
*Prostatic Neoplasms: PA, pathology
Tumor Cells, Cultured
RN 32222-06-3 (Calcitriol)
CN 0 (Calcium Channel Agonists)

L144 ANSWER 2 OF 17 MEDLINE on STN
AN 2000168596 MEDLINE
DN PubMed ID: 10706079
TI A calcitriol analogue, EB1089, inhibits the growth of LNCaP tumors in nude mice.
CM Comment in: Cancer Res. 2001 May 15;61(10):4294. PubMed ID: 11358859
AU Blutt S E; Polek T C; Stewart L V; Kattan M W; Weigel N L
CS Department of Molecular and Cellular Biology, Baylor College of Medicine, Houston, Texas 77030, USA.
NC CA58204 (NCI)
CA75337 (NCI)
SO Cancer research, **(2000 Feb 15)** 60 (4) 779-82.

Journal code: 2984705R. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200003
ED Entered STN: 20000330
Last Updated on STN: 20011025
Entered Medline: 20000320
AB Limited options for the treatment of prostate cancer have spurred the search for new therapies. One innovative approach is the use of 1alpha,25-dihydroxyvitamin D3 (calcitriol) analogues to inhibit cancer growth. We demonstrate here that the calcitriol analogue, EB1089, extensively inhibits the growth of LNCaP prostate cancer cells in culture and causes the cells to both accumulate in G0-G1 and undergo apoptosis. Importantly, we found that EB1089 inhibits the growth of LNCaP tumor xenografts in nude mice. Because of these antiproliferative properties in vivo, EB1089 is a potential new therapeutic agent for the treatment of prostate cancer.
CT Check Tags: Human; Male; Support, U.S. Gov't, P.H.S.
Animals
*Antineoplastic Agents: TU, therapeutic use
Apoptosis: DE, drug effects
*Calcitriol: AA, analogs & derivatives
Calcitriol: TU, therapeutic use
Calcium: BL, blood
Cell Cycle: DE, drug effects
Mice
Mice, Nude
***Prostatic Neoplasms: DT, drug therapy**
Prostatic Neoplasms: PA, pathology
Tumor Cells, Cultured
RN 134404-52-7 (seocalcitol); 32222-06-3 (Calcitriol); 7440-70-2 (Calcium)
CN 0 (Antineoplastic Agents)

L144 ANSWER 3 OF 17 MEDLINE on STN
AN 2000118058 MEDLINE
DN PubMed ID: 10639196
TI Calcium, lycopene, vitamin D and prostate cancer.
CM Comment on: Prostate. 1999 Sep 1;40(4):261-8. PubMed ID: 10420155
AU Grant W B
SO Prostate, **(2000 Feb 15)** 42 (3) 243.
Journal code: 8101368. ISSN: 0270-4137.
CY United States
DT Commentary
Letter
LA English
FS Priority Journals
EM 200002
ED Entered STN: 20000309
Last Updated on STN: 20000427
Entered Medline: 20000223
CT Check Tags: Human; Male
Anticarcinogenic Agents: TU, therapeutic use
*Calcium: ME, metabolism
*Carotenoids: TU, therapeutic use
Diet
Prostatic Neoplasms: DT, drug therapy
Prostatic Neoplasms: EP, epidemiology
*Prostatic Neoplasms: ET, etiology

Prostatic Neoplasms: PC, prevention & control
Vitamin D: ME, metabolism
***Vitamin D: TU, therapeutic use**
RN 1406-16-2 (Vitamin D); 36-88-4 (Carotenoids); 502-65-8 (lycopene); 7440-70-2 (Calcium)
CN 0 (Anticarcinogenic Agents)

=> d all l145 2 3 5

L145 ANSWER 2 OF 985 MEDLINE on STN
AN 2000507230 MEDLINE
DN PubMed ID: 11056493
TI Exploitable mechanisms for the blockade of androgenic action.
AU Griffiths K; Denis L J
CS Tenovus Cancer Research Centre, University of Wales College of Medicine, Cardiff, Wales, UK.
SO Prostate. Supplement, **(2000)** 10 43-51. Ref: 50
Journal code: 9003050. ISSN: 1050-5881.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200011
ED Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001115
CT Check Tags: Human; Male
*Androgen Antagonists: TU, therapeutic use
Drug Therapy, Combination
Enzyme Inhibitors: TU, therapeutic use
Estrogens: TU, therapeutic use
Finasteride: TU, therapeutic use
Forecasting
Intracellular Membranes: PH, physiology
***Prostatic Neoplasms: DT, drug therapy**
Protein-Tyrosine Kinase: AI, antagonists & inhibitors
Signal Transduction: PH, physiology
RN 98319-26-7 (Finasteride)
CN 0 (Androgen Antagonists); 0 (Enzyme Inhibitors); 0 (Estrogens); EC 2.7.1.112 (Protein-Tyrosine Kinase)

L145 ANSWER 3 OF 985 MEDLINE on STN
AN 2000507227 MEDLINE
DN PubMed ID: 11056490
TI Endocrine treatment: expected duration stage by stage.
AU Schroder F H
CS Department of Urology, Academic Hospital and Erasmus University, Rotterdam, The Netherlands.. vanalphen@urol.azr.nl
SO Prostate. Supplement, **(2000)** 10 26-31. Ref: 31
Journal code: 9003050. ISSN: 1050-5881.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200011

ED Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001115
CT Check Tags: Human; Male
*Androgen Antagonists: TU, therapeutic use
Disease Progression
***Estrogens: TU, therapeutic use**
Neoplasm Staging
*Prostate-Specific Antigen: BL, blood
*Prostatectomy
Prostatic Neoplasms: DT, drug therapy
Prostatic Neoplasms: IM, immunology
*Prostatic Neoplasms: PA, pathology
Prostatic Neoplasms: SU, surgery
*Prostatic Neoplasms: TH, therapy
Time Factors
CN 0 (Androgen Antagonists); 0 (Estrogens); EC 3.4.21.77 (Prostate-Specific Antigen)

L145 ANSWER 5 OF 985 MEDLINE on STN
AN 2000468915 MEDLINE
DN PubMed ID: 11022718
TI Revaluation of estrogen therapy on prostate cancer.
AU Takezawa Y; Kobayashi M; Yamanaka H
CS Department of Urology, Isesaki Municipal Hospital.
SO Nippon rinsho. Japanese journal of clinical medicine, **(2000 Jul)** 58 Suppl 223-7. Ref: 15
Journal code: 0420546. ISSN: 0047-1852.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW LITERATURE)
LA Japanese
FS Priority Journals
EM 200012
ED Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001212
CT Check Tags: Human; Male
Antineoplastic Agents, Hormonal: TU, therapeutic use
Diethylstilbestrol: TU, therapeutic use
***Estrogens: TU, therapeutic use**
Estrogens, Non-Steroidal: TU, therapeutic use
*Neoplasms, Hormone-Dependent: DT, drug therapy
***Prostatic Neoplasms: DT, drug therapy**
RN 56-53-1 (Diethylstilbestrol)
CN 0 (Antineoplastic Agents, Hormonal); 0 (Estrogens); 0 (Estrogens, Non-Steroidal)

=> d all l146 1-3

L146 ANSWER 1 OF 97 MEDLINE on STN
AN 2002005232 MEDLINE
DN PubMed ID: 11194670
TI [Radical prostatectomy with broadened scope of indications - analysis of early experience].
Radikalna prostatektomiia s razshireni pokazaniia - nachalen opit.
AU Chakarov S; Bechev R; Lazarov Z; Fachikov Ts; Rangelov S
CS Government University Hospital "St Anna," Urologic Clinic, Medical

University, Sofia, Bulgaria.
SO Khirurgiia, **(1999)** 55 (3) 47-8.
Journal code: 0376355. ISSN: 0450-2167.
CY Bulgaria
DT Journal; Article; (JOURNAL ARTICLE)
LA Bulgarian
FS Priority Journals
EM 200201
ED Entered STN: 20020121
Last Updated on STN: 20020128
Entered Medline: 20020123
CT Check Tags: Human; Male
Acid Phosphatase: AN, analysis
Acid Phosphatase: BL, blood
Aged
Androgen Antagonists: TU, therapeutic use
Antineoplastic Agents, Hormonal: TU, therapeutic use
Biopsy
Flutamide: TU, therapeutic use
Goserelin: TU, therapeutic use
Middle Aged
Prostate-Specific Antigen: BL, blood
*Prostatectomy: MT, methods
Prostatic Neoplasms: DI, diagnosis
Prostatic Neoplasms: DT, drug therapy
Prostatic Neoplasms: SC, secondary
*Prostatic Neoplasms: SU, surgery
RN 13311-84-7 (Flutamide); 65807-02-5 (Goserelin)
CN 0 (Androgen Antagonists); 0 (Antineoplastic Agents, Hormonal); EC 3.1.3.2 (Acid Phosphatase); EC 3.4.21.77 (Prostate-Specific Antigen)

L146 ANSWER 2 OF 97 MEDLINE on STN
AN 2001155404 MEDLINE
DN PubMed ID: 11168686
TI Prostate cancer with multiple lung metastases in a hemodialysis patient.
AU Hayakawa K; Matsumoto M; Aoyagi T; Miyaji K; Hata M
CS Department of Urology, Tokyo Dental College, Ichikawa General Hospital, Chiba, Japan.. hayakawa@tdc.ac.jp
SO International journal of urology : official journal of the Japanese Urological Association, **(2000 Dec)** 7 (12) 464-6.
Journal code: 9440237. ISSN: 0919-8172.
CY Australia
DT (CASE REPORTS)
Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200103
ED Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010322
AB In hemodialysis patients, few cases of prostate cancer have been reported until recently. We present a case of prostate cancer with multiple lung metastases in a chronic hemodialysis patient. A 65-year-old Japanese man who had maintained hemodialysis for 5 years was referred to our hospital with multiple metastatic lung tumors. Serum prostate tumor markers were highly elevated although his plasma testosterone level was within the normal range. A transrectal needle prostate biopsy confirmed a histologic diagnosis of moderately differentiated adenocarcinoma. Androgen blockade therapy was very effective as evidenced by a quick decrease of serum tumor markers. The follow-up computed tomography scan of the chest performed 3

months later showed a complete disappearance of the coin lesions. The early detection of prostate cancer in hemodialysis patients is difficult because of a lack of urologic symptoms, which indicate the importance of periodic screening by serum tumor markers. Combined androgen blockade is effective even in hemodialysis patients. However, close follow up is necessary because long-term results and prognoses are still unknown.

CT Check Tags: Human; Male
Adenocarcinoma: DT, drug therapy
*Adenocarcinoma: PA, pathology
Adenocarcinoma: RA, radiography
*Adenocarcinoma: SC, secondary
Aged
Androgen Antagonists: TU, therapeutic use
Antineoplastic Agents, Hormonal: TU, therapeutic use
Drug Therapy, Combination
Flutamide: TU, therapeutic use
Goserelin: TU, therapeutic use
Lung Neoplasms: RA, radiography
*Lung Neoplasms: SC, secondary
Prostatic Neoplasms: DT, drug therapy
*Prostatic Neoplasms: PA, pathology
Radiography, Thoracic
*Renal Dialysis
Tomography, X-Ray Computed

RN 13311-84-7 (Flutamide); 65807-02-5 (Goserelin)
CN 0 (Androgen Antagonists); 0 (Antineoplastic Agents, Hormonal)

L146 ANSWER 3 OF 97 MEDLINE on STN
AN 2001006516 MEDLINE
DN PubMed ID: 11010743
TI Goserelin and locally advanced prostate cancer: new indication. Pros and cons.
AU Anonymous
SO Prescrire international, **(2000 Jun)** 9 (47) 75-6.
Journal code: 9439295. ISSN: 1167-7422.
CY France
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Health Technology
EM 200009
ED Entered STN: 20010223
Last Updated on STN: 20010223
Entered Medline: 20000922
AB (1) Goserelin, a GnRH agonist, has a new licensed indication in France, as an adjuvant to external radiotherapy for locally advanced prosate cancer. (2) The clinical file in this indication includes two trials of satisfactory methodological quality comparing radiotherapy + goserelin with radiotherapy alone. (3) In these trials the radiotherapy + goserelin combination increased the specific-symptom-free survival time. (4) In one trial goserelin caused endocrine disorders in 19% of patients. There were also more cases of urinary incontinence (13% in absolute values) among patients receiving the radiotherapy + goserelin combination. Furthermore, goserelin almost always causes impotence and reduced libido.
CT Check Tags: Comparative Study; Human; Male
Aged
Antineoplastic Agents, Hormonal: AD, administration & dosage
Antineoplastic Agents, Hormonal: AE, adverse effects
Antineoplastic Agents, Hormonal: TU, therapeutic use
Clinical Trials
Endocrine Diseases: CI, chemically induced

France
Gonadorelin: AG, agonists
*Goserelin
Goserelin: AD, administration & dosage
Goserelin: AE, adverse effects
Goserelin: TU, therapeutic use
Impotence: CI, chemically induced
Libido: DE, drug effects
*Prostatic Neoplasms
Prostatic Neoplasms: DT, drug therapy
Prostatic Neoplasms: RT, radiotherapy
Treatment Outcome
Urinary Incontinence: CI, chemically induced
RN 33515-09-2 (Gonadorelin); 65807-02-5 (Goserelin)
CN 0 (Antineoplastic Agents, Hormonal)

=> d all l147 2 3 5

L147 ANSWER 2 OF 11 MEDLINE on STN
AN 90282023 MEDLINE
DN PubMed ID: 2191570
TI Clinical studies on endocrine therapy of prostatic carcinoma (2): Prognosis of patients with prostatic carcinoma given endocrine therapy, and analyses of causes of death and side effects of endocrine therapy.
AU Kumamoto Y; Tsukamoto T; Umehara T; Shimazaki J; Fuse H; Oshima H; Takeuchi H; Yoshida O; Okada K; Saito Y; +
CS Department of Urology, Sapporo Medical College.
SO Hinyokika kiyo. Acta urologica Japonica, **(1990 Mar)** 36 (3) 285-93.
Journal code: 0421145. ISSN: 0018-1994.
CY Japan
DT (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
LA Japanese
FS Priority Journals
EM 199007
ED Entered STN: 19900824
Last Updated on STN: 19900824
Entered Medline: 19900719
AB Of 572 patients with prostatic carcinoma, 497 received endocrine therapy as the initial treatment. These patients were surveyed in a cooperative research study by members from five universities. Prognosis, causes of death and side effects of estrogen therapy were studied. The prognosis of patients who had received endocrine therapy became worse, as the stage progressed. The prognosis of those who had received a combination of estrogen therapy with castration tended to be better than that of those who had received estrogen therapy alone. Similarly, the prognosis of those who had received a combination of progesterone therapy with castration tended to be better than that of those who had had progesterone therapy alone. No relationship was found between estrogen doses (low, medium and high) and prognosis, although a precise comparison among the three could not be made because of the smaller number of patents with low doses. A high dose of estrogen may not always be the indication, rather a medium dose such as 300 mg diethylstilbestrol diphosphate may be clinically appropriate. The cause of death could be identified in 303 patients who had received endocrine therapy. Cancer-related death was the most frequent (63.7%), and cardio- or cerebrovascular death accounted for only 14.2% of the cases. When this analysis was confined to the patients

who had received estrogen therapy, estrogen administration seemed to be the cause of cardio- or cerebrovascular death of 16.1% of the patients. Daily dosing of estrogen was not definitely related to the incidence, or the interval to cardio- or cerebrovascular death. However, among the patients who had died of cardio- or cerebrovascular disease, 50% of the patients who had received a medium or high dose of estrogen tended to die within two years after treatment, while 50% of those who had received a low dose died within three years.

CT Check Tags: Human; Male; Support, Non-U.S. Gov't
Cause of Death
English Abstract
Estrogens: AE, adverse effects
*Estrogens: TU, therapeutic use
Japan: EP, epidemiology
Multicenter Studies
*Neoplasms, Hormone-Dependent: DT, drug therapy
Neoplasms, Hormone-Dependent: EP, epidemiology
Neoplasms, Hormone-Dependent: MO, mortality
Progesterone: AE, adverse effects
***Progesterone: TU, therapeutic use**
Prognosis
***Prostatic Neoplasms: DT, drug therapy**
Prostatic Neoplasms: EP, epidemiology
Prostatic Neoplasms: MO, mortality

RN 57-83-0 (Progesterone)
CN 0 (Estrogens)

L147 ANSWER 3 OF 11 MEDLINE on STN
AN 89382122 MEDLINE
DN PubMed ID: 2570857
TI A new approach to prostate cancer.
AU Ito Y Z; Nakazato Y; Petrow V
CS College of Medical Care and Technology, Gunma University, Department of Pathology, Gunma University School of Medicine, Japan.
SO Journal of pharmacy and pharmacology, **(1989 Jul)** 41 (7) 488-9.
Journal code: 0376363. ISSN: 0022-3573.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198910
ED Entered STN: 19900309
Last Updated on STN: 19950206
Entered Medline: 19891020
AB Growth of androgen-dependent human prostatic adenocarcinoma implanted in the nude mouse (Honda tumour), is inhibited by 6-methyleneprogesterone. This steroid is a potent inhibitor of both rat and human prostatic 5 alpha-reductase in-vitro. In-vivo, at the studied dose level, it reduces metabolic conversion of testosterone to dihydrotestosterone with minimal effects upon circulating LH and testosterone. These data support the hypothesis that dihydrotestosterone and not testosterone is the main trophic androgen of the human prostatic neoplasm.
CT Check Tags: Human; Male; Support, Non-U.S. Gov't
*Adenoma: DT, drug therapy
Adenoma: PP, physiopathology
Animals
Disease Models, Animal
Mice
Mice, Nude
Neoplasm Transplantation

Organ Weight: DE, drug effects
*Progesterone: AA, analogs & derivatives
Progesterone: TU, therapeutic use
Prostate: DE, drug effects
***Prostatic Neoplasms: DT, drug therapy**
Prostatic Neoplasms: PP, physiopathology
Seminal Vesicles: DE, drug effects
RN 19457-57-9 (6-methylene-4-pregnene-3,20-dione); 57-83-0 (Progesterone)

L147 ANSWER 5 OF 11 MEDLINE on STN
AN 80229109 MEDLINE
DN PubMed ID: 6156222
TI Treatment of metastatic bone cancer.
AU Fukuma H
SO Nippon Seikeigeka Gakkai zasshi, **(1980 Apr)** 54 (4) 403-11.
Journal code: 0413716. ISSN: 0021-5325.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
LA Japanese
FS Priority Journals
EM 198009
ED Entered STN: 19900315
Last Updated on STN: 19900315
Entered Medline: 19800923
CT Check Tags: Female; Human; Male
Adult
Aged
Androgens: TU, therapeutic use
Bone Neoplasms: DT, drug therapy
*Bone Neoplasms: SC, secondary
Bone Neoplasms: SU, surgery
Breast Neoplasms: DT, drug therapy
Breast Neoplasms: SU, surgery
Estrogens: TU, therapeutic use
Fracture Fixation, Internal
Laminectomy
Middle Aged
Palliative Care
Progesterone: TU, therapeutic use
Prostatic Neoplasms: DT, drug therapy
Prostatic Neoplasms: SU, surgery
RN 57-83-0 (Progesterone)
CN 0 (Androgens); 0 (Estrogens)

=> d all l148 1 3 4

L148 ANSWER 1 OF 107 MEDLINE on STN
AN 2002341685 MEDLINE
DN PubMed ID: 12084334
TI Neoadjuvant hormone therapy before radical prostatectomy does not improve disease-specific survival.
AU Steiner M S
CS Department of Urology, University of Tennessee, Memphis, 956 Court Avenue, Room H216, Memphis, TN 38163, USA.. Msteiner@utmem.edu
SO Current urology reports, **(2000 May)** 1 (1) 7-8.
Journal code: 100900943. ISSN: 1527-2737.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English

FS Priority Journals
EM 200302
ED Entered STN: 20020627
Last Updated on STN: 20030226
Entered Medline: 20030225
CT Check Tags: Human; Male
*Antineoplastic Agents, Hormonal: TU, therapeutic use
Chemotherapy, Adjuvant
***Leuprolide: TU, therapeutic use**
Preoperative Care
*Prostatectomy
***Prostatic Neoplasms: DT, drug therapy**
*Prostatic Neoplasms: MO, mortality
Prostatic Neoplasms: SU, surgery
Survival Rate
RN 53714-56-0 (Leuprolide)
CN 0 (Antineoplastic Agents, Hormonal)

L148 ANSWER 3 OF 107 MEDLINE on STN
AN 2001110504 MEDLINE
DN PubMed ID: 11096250
TI Expression of estrogen receptor alpha and beta mRNAs in prostate cancers treated with leuprorelin acetate.
AU Maruyama S; Fujimoto N; Asano K; Ito A; Usui T
CS Department of Cancer Research, Research Institute for Radiation Biology and Medicine (RIRBM), Hiroshima University, Hiroshima, Japan.
SO European urology, **(2000 Nov)** 38 (5) 635-9.
Journal code: 7512719. ISSN: 0302-2838.
CY Switzerland
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200102
ED Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010202
AB OBJECTIVE: The discovery of a novel estrogen receptor (ER), ER-beta, has given rise to new possibilities regarding estrogen's roles in the prostate. Although ER-beta is reported to be expressed preferentially in the rat prostate, its expression in the human prostate and relationship to cancer development has not been investigated. Thus the purpose of the study was to examine mRNA levels of ER-alpha and ER-beta in benign prostatic hyperplasia and prostate carcinoma. METHODS: Samples of 15 prostate cancers obtained at radical prostatectomy were examined. All the patients had been maintained on androgen withdrawal therapy for at least 3 months. ER-alpha and ER-beta mRNAs were measured with a competitive PCR technique. RESULTS: Both ER-alpha and ER-beta mRNAs were detected in all of the prostate cancer tissues examined, as well as in PC3 and LNCap cells, although the levels varied among specimens. Interestingly, both types were significantly decreased in cases with lymph node metastasis. However, there was no correlation between ER mRNA levels and any other clinicopathological parameters. CONCLUSIONS: (1) Both ER-alpha and ER-beta mRNAs are expressed in prostate cancer and (2) expression of ER mRNA may not be related to cancer progression but may be negatively correlated with metastasis.
CT Check Tags: Human; Male; Support, Non-U.S. Gov't
Aged
Aged, 80 and over
*Antineoplastic Agents, Hormonal: TU, therapeutic use
*Gene Expression Regulation, Neoplastic

***Leuprolide: TU, therapeutic use**
Middle Aged
*Prostatic Hyperplasia: GE, genetics
***Prostatic Neoplasms: DT, drug therapy**
*Prostatic Neoplasms: GE, genetics
*RNA, Messenger: BI, biosynthesis
*Receptors, Estrogen: GE, genetics
RN 53714-56-0 (Leuprolide)
CN 0 (Antineoplastic Agents, Hormonal); 0 (RNA, Messenger); 0 (Receptors, Estrogen); 0 (estrogen receptor alpha); 0 (estrogen receptor beta)

L148 ANSWER 4 OF 107 MEDLINE on STN
AN 2001029973 MEDLINE
DN PubMed ID: 10887633
TI Leuprolide implant approved for once-yearly palliative treatment of advanced prostate cancer.
AU Anonymous
SO Oncology (Williston Park, N.Y.), **(2000 Jun)** 14 (6) 828, 830. Journal code: 8712059. ISSN: 0890-9091.
CY United States
DT News Announcement
LA English
FS Priority Journals
EM 200011
ED Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001121
CT Check Tags: Human; Male
*Antineoplastic Agents, Hormonal: AD, administration & dosage
Antineoplastic Agents, Hormonal: AE, adverse effects
Antineoplastic Agents, Hormonal: TU, therapeutic use
Drug Approval
Drug Implants
*Leuprolide: AD, administration & dosage
Leuprolide: AE, adverse effects
Leuprolide: TU, therapeutic use
Palliative Care
***Prostatic Neoplasms: DT, drug therapy**
United States
United States Food and Drug Administration
RN 53714-56-0 (Leuprolide)
CN 0 (Antineoplastic Agents, Hormonal); 0 (Drug Implants)

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